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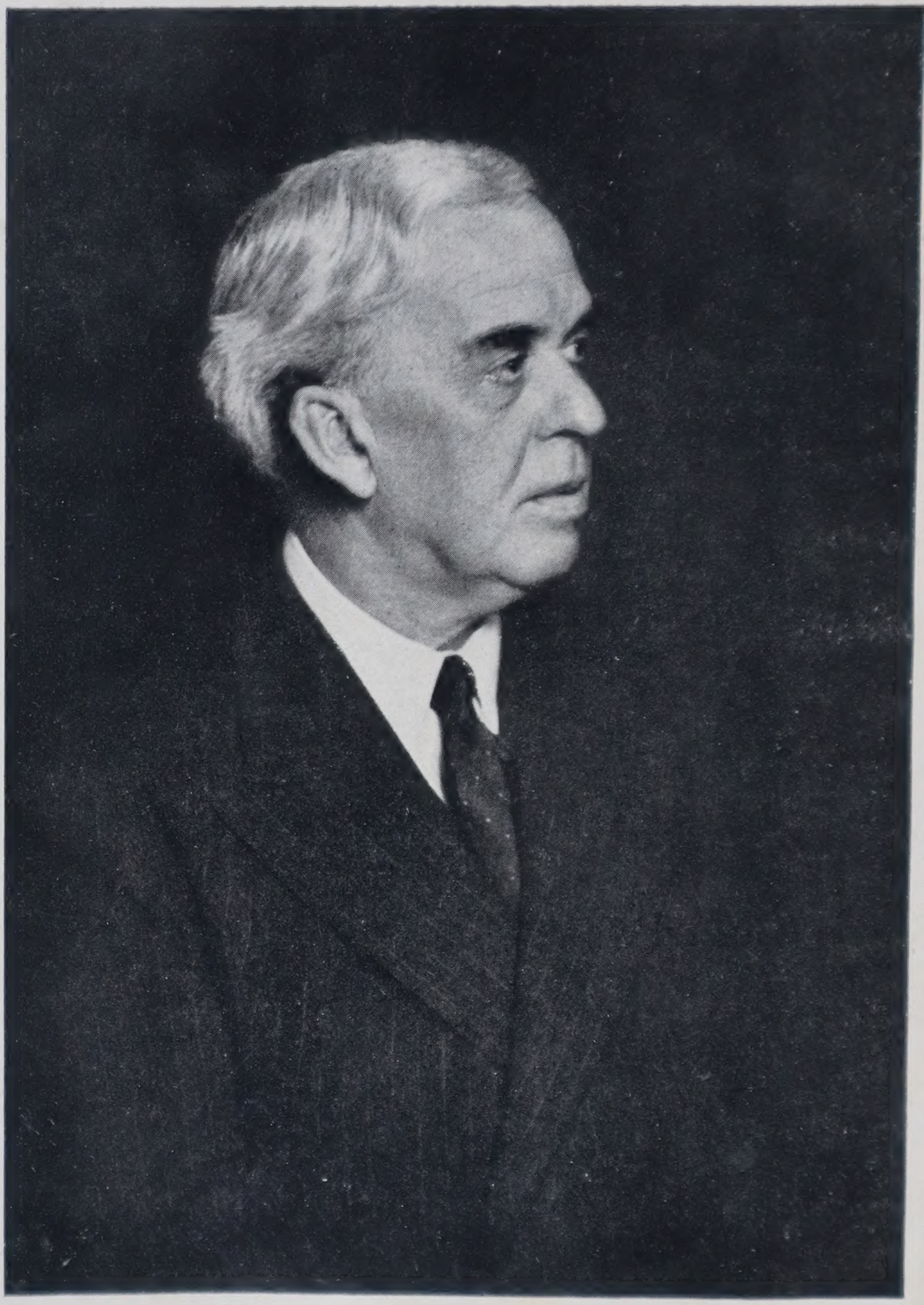
The Work of Sir Robert McCarrison



The Work of Sir Robert McCarrison

edited by

H. M. SINCLAIR

with additional introductory essays by

W. R. AYKROYD and E. V. McCOLLUM

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Bust by the late K. (Kathleen) Scott (Lady Kennet)
Widow of Captain Scott, R.N.
Married Lord Kennet, 1922
She died in 1947

Preface

Major-General Sir Robert McCarrison, C.I.E., M.A., M.D., D.Sc., LL.D., F.R.C.P., B.AO., was born on 15th March 1878. After qualifying medically in Ireland in 1900, he entered the Indian Medical Service the following year and spent most of the next third of a century in India. His nutritional researches there were published in many scientific papers and nine books; the papers are not always readily accessible and the books are mainly out of print. Yet those engaged in nutritional research must repeatedly refer to them, and therefore the suggestion arose—initially from an outstandingly competent Indian in this field—that the more important contributions should be reprinted.

The imminence of Sir Robert's seventy-fifth birthday made the reprinting particularly appropriate. But such a *Festschrift* should contain more than reprinted papers: it should also mention the contemporary setting in which the work was done, the immediate effects of that work, and the importance of it in the light of present-day knowledge. There was no one better qualified to write of the impact of McCarrison's work than Dr. E. V. McCollum, Emeritus Professor of Biochemistry in the Johns Hopkins University, who had himself made such classical contributions to nutritional research. In accepting this assignment Dr. McCollum wrote: 'How well I remember the enthusiasm with which I presented, year by year, the researches of McCarrison to my classes of students. It will give me a thrill to go through his publications again.'

McCarrison's name will always be associated with the Nutrition Research Laboratories at Coonoor, which he founded and of which he was the first Director. The present Director, Dr. V. N. Patwardhan, has recently published a delightful history of these Laboratories, and he has pointed out that 'It is no exaggeration to say that it was the genius and sustained efforts of McCarrison as also the foresight and generosity of the Indian Research Fund Association which sponsored McCarrison's researches that resulted in the unit for nutritional research which gradually developed into a full fledged institution.' And in a Foreword to Patwardhan's history, the Minister of Health of the Government of

India (Hon. Rajkumari Amrit Kaur) wrote: 'As in the case of most achievements of enduring value the development of this laboratory into an institution with its outstanding position in the field of nutrition research in the East is due, to a considerable extent, to the impetus given to it by its Founder-Director, Sir Robert McCarrison, whose contributions to the study of nutrition problems and to the stimulation of interest in this sphere of research have earned for him the lasting gratitude of India.' When he retired in 1935, McCarrison was succeeded as Director by Dr. W. R. Aykroyd, now Director of the Nutrition Division of the Food and Agriculture Organization of the United Nations. Dr. Aykroyd has contributed an essay upon the Laboratories at Coonoor.

Nutritional science advances with rapid strides. The broad problems McCarrison tackled have been further elucidated by recent research, much of it done in the Coonoor Laboratories. Mr. Taylor and I have endeavoured to add a postscript to his work. It seemed best to reprint the selected papers as published, omitting the passages that were redundant or repetitive, and making only occasional minor editorial corrections. All illustrations have had to be left out; but those wishing to consult the original papers will be aided by the bibliography at the end of the volume. Miss Joyce Buxton has rendered invaluable aid in assisting with this editorial work, and she and Miss Barbara Yeates have checked the proofs against the original papers. A special word of appreciation is due to Messrs. Faber & Faber Limited, and in particular to Mr. Richard de la Mare, for their keen interest in undertaking the production of the book and their skilful speed which ensured it would arrive at the right time.

It remains to add that the authors of the three introductory essays, and the publishers, know they are not alone but will be joined by scientists on both sides of the Atlantic and especially in India when they offer to Sir Robert McCarrison, with this book, their greetings upon his seventy-fifth birthday and their appreciation of his long period of distinguished work.

H. M. SINCLAIR

Magdalen College, Oxford,
October 1952

PROLOGUE

1. The Nutrition Research Laboratories, Coonoor

by W. R. AYKROYD, M.D., Sc.D.

Director of the Laboratories, 1935–45
Director of the Nutrition Division, FAO

Coonoor is situated in the Nilgiris or Blue Mountains in South India, at an altitude of 5–6,000 feet above sea-level. It lies on the southern rim of the Nilgiris, where the plateau ends abruptly in cliffs which fall almost sheer for several thousand feet to the Coimbatore plains. The approach to Coonoor from the south is more than picturesque. From Mettupalayam—the terminus of the broad-gauge railway from Madras—the mountain road and railway wind upwards through fragrant betel-nut plantations, through tropical forests which at some seasons blaze with the colour of flowering trees, through rocky gorges and across mountain streams, and finally through coffee and tea estates into the Coonoor bazaar, which is something of an anti-climax. Even long familiarity cannot blunt the traveller's pleasure in the sight of the tremendous escarpment of the Nilgiris seen from the Blue Mountain Express in the early morning, a pleasure enhanced by the thought of the coolness at the mountain-top.

The Nilgiri plateau is a great mass of archean rock covered by shallow and easily eroded soil. Its oldest inhabitants are the Todas, a pastoral people of dim origins practising polyandry, who have probably been more exposed to investigation by anthropologists than any other primitive group anywhere in the world. The Badagas, an agricultural community originating in Mysore, are more recent arrivals: they were driven from Mysore a few hundred years ago by the predecessors of Tipu Sultan and took refuge in the Nilgiris. The British penetrated the Nilgiris early in the nineteenth century. The young officers who first reached the high plateau, after making their way through the intensely malarious foothills, were greatly surprised at the mildness of the climate. It is said that their reports on this subject were not believed by their seniors, who regarded a temperate climate in South India as contrary to nature. The results of some hundred years of British occupation—as visible in the nineteen-twenties and thirties—included a hot-weather station for the Government of Madras at Ootacamund with appropriate secretarial offices and a government house in Scotch baronial style, extensive tea plantations producing some of the best tea in the world, a gunpowder factory, a military cantonment, two golf courses and a jackal hunt, and numerous bungalows inhabited by retired English officials which bore names such as 'Balmoral' and 'Strathearn' and were surrounded by gardens famous for their roses.

The Pasteur Institute of Southern India was built in Coonoor in 1906 for the production of anti-rabies vaccine and the treatment of patients with rabies. It was located in the hills because it was felt that scientific workers and laboratory animals would thrive better in the hills than on the plains. In 1918, Lieut.-Col. McCarrison secured an empty room in this building and began work with one untrained assistant and very limited equipment.

So much for the unusual background of the institution which grew into the Nutrition Research Laboratories.

McCarrison's earliest investigations in Coonoor were officially called the 'Beri-beri Inquiry' and were financed by the Indian Research Fund Association, a body corresponding to the Medical Research Council in the United Kingdom. While this was for practical purposes his first opportunity to undertake full-time research on problems of nutrition, he had been interested in the subject for many years. When serving as a young I.M.S. officer in Gilgit and elsewhere on the frontiers of Northern India, he had been struck by the fine physique, powers of endurance and relative freedom from disease of certain of the peoples with whom he came into contact and had conceived the idea that these characteristics might be related to their diet—a diet based on wholemeal flour, milk products, vegetables and fruits, with a little meat on festive occasions. A closely similar idea was put forward by D. McCay in 1912, in a book called *The Protein Element in Nutrition*; McCay suggested that the differences in physique between the peoples of Northern India and those of East, Central and South India were due to differences in diet. McCarrison had also carried out field and laboratory research in Kasauli in 1912 and 1913 on the relation between goitre, diet and infection. It is clear that when he began work in Coonoor he had formulated the hypothesis that health and physical development are dependent on diet to an extent unrealized at that time by orthodox medicine and physiology, and wished to put this hypothesis to the test. The proposed investigations were no doubt designated the 'Beri-beri Inquiry' because it was customary for inquiries financed by the I.R.F.A. to be related to the study of a specific disease. McCarrison's ideas had, however, a much wider range.

When Pasteur's fundamental discoveries had opened a new era in medicine, and indeed in world history, great success had been achieved in India in the investigation of bacterial and parasitic disease. The demonstration by Ross of the life-cycle of the malaria parasite had been followed up by other distinguished workers who clarified the epidemiology of malaria and gave India a leading position in malaria research. Important pioneer work had been done on plague, kala-azar, cholera, the dysenteries and other diseases. In these investigations I.M.S. officers had played a notable part. McCarrison himself had followed the tradition of the service during his early days in India. When in Chitral, in 1902–4, he investigated a 'three-day fever' prevalent in this area and rightly suggested that the causative organism was transmitted by the sand-fly and that the fever would be found in other parts of India.

The nutrition research unit established in the Pasteur Institute in 1918 was thus a new departure. Prevailing trends of medical research in India lay in other directions. As far as nutrition research is concerned, no very striking contributions had been made in India. A few epidemiological studies of beri-beri were made in the nineteenth century, the most important of which was that of Malcolmson, dated as early as 1835. Epidemic dropsy and 'burning feet' had been described, but their causation was unknown. The Famine Inquiry Commissions established to report on the great famines which occurred between 1870 and the end of the century were struck by the fact that mortality from various common diseases enormously increased during periods of food shortage and famine, but their findings had not been related to ordinary conditions of life in India—i.e. to the chronic undernourishment which affected and affects a large part of the population at the best of times. By and large, no work in the field of nutrition had been done which bore comparison with the classical investigations of Eijkman and his colleagues in Java.

The work of the 'Beri-beri Inquiry' proceeded until January 1920, when McCarrison was invalided home to England. There he was soon joined by his assistant, Sub-Assistant Surgeon Mula Singh, who was given some further training in Oxford in histological techniques. His research work, particularly his investigations of the problems of goitre, had become widely known, and in 1921 he was invited to deliver a series of lectures in the U.S.A., amongst which were the de Lamar Lecture in Baltimore, the Mellon Lecture in Philadelphia, a Mayo Foundation Lecture in Rochester, and the Mary Scot Newbold Lecture in Philadelphia. He returned in 1922 to Coonoor to resume work, but not for long. The 'Beri-beri Inquiry' was 'axed' in November 1923 on the recommendation of the Government of India, which was at that time suffering from one of its periodic economy scares and was unimpressed by the results of the Inquiry and the interest and acclamation with which they had been received by scientific audiences abroad. The subordinate personnel of the Inquiry was dispersed.

In 1925 wiser counsels prevailed and the Coonoor nutrition research unit was re-established, this time under the broader title of the 'Deficiency Disease Inquiry'. The 'Deficiency Disease Inquiry' survived until 1929, when its name was changed to 'Nutrition Research', McCarrison being appointed as Director. The title 'Nutrition Research Laboratories' was introduced shortly after this. McCarrison continued as Director until 1935.

With the change in title in 1929 the research unit assumed the general shape and functions which it still retains. In proposing to the Governing Body, I.R.F.A., the establishment of 'Nutrition Research', McCarrison outlined its objective as follows:

'(a) The investigation of the Fundamental Science of Nutrition and of Applied Nutrition.
(b) The study of the agricultural aspects of nutrition.
(c) The determination of the food values of various food materials in general and in India.
(d) Investigations designed to make good the deficiencies of vegetable oils when these are used as substitutes for butter.
(e) The study of the effects of faulty foods, in their infinite variety of combination, on the animal organism as a whole and on certain organs and tissues of the body in particular.
(f) The experimental production and the determination of the cause of specific diseases: pernicious anaemia, dropsy, scurvy-oedema, beri-beri, new growths in the stomach, gastro-intestinal diseases, stone in the bladder and its sequalae.

In addition to these activities, the Deficiency Diseases Inquiry is now regarded by many official and private bodies, and by the public, as a Central Information Bureau to which they are entitled to apply as need be.'

Apart from the record of research, the status of the research unit was improved by the findings of the Royal Commission on Agriculture. The Commission—under the chairmanship of the late Lord Linlithgow, subsequently to be Viceroy—visited Coonoor in 1926 and was suitably impressed by the importance of McCarrison's work and its bearing on agriculture. It recommended the establishment of a central and per manent institution devoted to research on human nutrition. Lord Linlithgow was keenly interested in nutrition, and when Viceroy supported the development of nutrition research and its practical application. On several occasions he summoned the Director of the Laboratories to viceregal headquarters to discuss the subject with him and in 1942 paid a further visit to Coonoor. Another outcome of the Commission's visit is worthy of mention. One of its members, the Rajah of Parlakimedi, after listening to McCarrison's exposition, presented the research unit with a lakh of rupees 'across the table' (100,000 rupees or £7,000). This was used for the creation of two Parlakimedi Research Fellowships, the first fellowships in India supported by a private donation. The Parlakimedi research fellows were later a useful addition to the staff of Laboratories.

The period 1928 to 1935 was one of steady growth. The scientific staff was increased by the appointment of two qualified Indian workers, S. Ranganathan, a chemist, and G. Sankaran, a biochemist. McCarrison had also the services of Sub-Assistant Surgeon B. G. Krishnan, who had been among his first assistants, following the fortunes of the research unit during its early disjointed phase. The subordinate staff of attendants and 'menials' needed for expansion was recruited and trained. More rooms were obtained in the Pasteur Institute and equipped with scientific apparatus. During these years, in fact, the Nutrition Research Laboratories became a recognized and firmly established institution.

It is not the author's task to assess the importance of McCarrison's contributions to the science of nutrition. But an account of the trends of research in the Coonoor unit during the various stages of its existence is a necessary part of this historical review. A list of papers published from the unit from 1919 to 1945 was prepared in 1946 by R. Passmore. This shows that from 1919 to 1924 McCarrison was interested mainly in the 'pathogenesis of deficiency disease'; out of twenty-three papers published during this period, fourteen bore this general title. The earliest work of the Beri-beri Inquiry was largely concerned with the pathological changes caused by defective diets in various organs in pigeons and monkeys. The defective diets used in these and many later experiments were combinations of natural foods. In much subsequent work in Coonoor diets of this kind, in particular diets resembling those consumed by human communities, were given to experimental animals. This method of research, in the author's opinion, often provides most valuable information, though it may not appeal to the meticulous scientific worker who prefers highly purified and highly artificial diets of precisely known and reproducible composition.

The Nutrition Research Laboratories, Coonoor

One publication specifically relating to beri-beri was produced by the Beri-beri Inquiry. This was entitled 'The Relationship of Rice to Beri-beri in India' and was written in 1923 by McCarrison in collaboration with R. V. Norris. On the basis of his experiments, supported by Norris's chemical analyses, they suggested that beri-beri was not due to a complete absence of vitamin B in the diet; no human diets are entirely devoid of this vitamin. Attacks of beri-beri occur when intake of the vitamin is reduced by special circumstances or when the need for it is increased, e.g. by coincident infectious disease. In the course of this investigation the important observation was made that washing greatly reduces the vitamin content of ordinary rice.

Numerous papers directly or indirectly concerned with goitre were published between 1927 and 1935. The results of a long series of experiments were presented in *The Life Line of the Thyroid Gland—a Contribution to the Study of Goitre* by McCarrison and Madhava, published in 1932. McCarrison during this period was particularly interested in goitrogenic substances, the role of which in the production of human goitre has not yet been fully clarified.

Bladder stone is prevalent in certain parts of India, particularly in the north, occurring not only in adults but also very frequently in children. It is more common among wheat-eaters than rice-eaters. McCarrison felt that the condition as seen in India was in some way associated with diet. There was some experimental evidence from elsewhere that bladder stone could occur in rats as a result of vitamin A deficiency. McCarrison devised a method of producing stone in rats by giving diets containing various combinations of calcium and phosphorus salts. He also showed that under certain experimental conditions wheat is more 'stone-producing' than other cereals. How far the urinary deposits produced in rats by various means in this long series of experiments were analogous to stone in the bladder in man remained, however, doubtful.

Further work was done on deficiency of thiamine in pigeons. Other subjects of research included gastric ulcer and lathyrism. It was found impossible to reproduce lathyrism in rats by feeding them on *lathyrus sativus*.

While occupied in these detailed investigations, McCarrison did not lose his interest in the general relation between diet, health and disease, which was in fact the mainspring of his work. One of his experiments with a bearing on this subject became famous throughout India. Groups of rats were fed on diets resembling those eaten by different Indian communities—Sikhs, Bengalis, Madrassis and others. The rats fed on the Sikh diet, composed of whole wheat, milk in abundance, sprouted dhal, vegetables and bone with a little meat, far exceeded in growth those given the 'poor rice diets' characteristic of the east and south of India. This corresponded in general with the physical development of the human communities; there is an unquestionable decline in physique from the north-west to the east and from the north to the south of the Indian peninsula. It is recorded that McCarrison, in demonstrating the results of these experiments to visitors, was wont to draw their attention to his first and chief assistant, Sirdar Bahadur Mula Singh, a black-bearded Sikh of magnificent proportions illustrating in his person all the advantages of a properly-constituted diet.

Within the same field of interest were the broad comparisons drawn between the vital statistics of rats fed on a good diet and on various kinds of bad diet. The good diet was the Sikh diet, which became the normal diet of the stock rat colony; on their milk and whole wheat chappaties the animals throve, produced large and healthy litters and were free from disease. On the bad diets, both natural and synthetic, what a difference! A high infantile mortality, with a tendency on the part of mother rats to eat their young, rough and mangy fur, a lean and hungry look, diseases of many kinds and premature death—these were among the results of improper feeding. When I took charge of the Laboratories I was told that the rats fed on the Sikh diet—later known as the McCarrison diet—never died from natural causes. I received this statement with proper scepticism, but in due course became convinced that it was true. In fact, it became later the custom, in teaching students, to exhibit a litter of one-day-old rats and stake the reputation of the Laboratories on their survival until weaning time in perfect health. The mother rat, whether conscious or not of her responsibilities, never failed in her duty.

The Coonoor Laboratories were frequently visited by missionaries recuperating from the heat in the Nilgiri hills. McCarrison, it is said, sometimes told missionaries that he was himself a missionary and had an appropriate text to preach from. This was: 'Hearken diligently unto me and eat ye that which is good' (Isaiah lv, 2). Certainly a walk round the Laboratories with McCarrison almost invariably led to conversion. To spread the gospel more widely, he wrote in 1928 a popular book called *Food*, which cost eight annas, achieved a large circulation and was translated into several Indian languages. *Food* was written for children but generally read by adults.

In 1935 McCarrison retired from India but not from active work. I was appointed to succeed him and held the post of Director for ten years. Since the activities of any research institute are influenced by the background and experience of its director, a few biographical facts may be given. I first became interested in nutrition when working in Newfoundland in 1926 and 1927; direct experience in that country seemed to show that a faulty diet (bread, salt meat, molasses and tea) leads not only to food deficiency disease but also to much general ill health and sickness of diverse kinds. Later I worked as Beit Memorial Research Fellow in the Lister Institute in London under Sir Charles Martin and Dr. Hariette Chick; here some investigations on the thiamine content of raw and parboiled rice gave me an interest in problems of nutrition among rice-eaters. In 1930 I joined the Health Section of the League of Nations in Geneva, taking the first international appointment specifically concerned with nutrition. The importance of nutrition to public health was becoming more and more clear at that time and it was felt that an international health organization should include a 'nutrition officer'. 'Nutrition and public health' was the main theme of my activities as a member of the League Secretariat.

In 1935 the Nutrition Research Laboratories were a going concern—an adequately staffed and equipped nutrition research institute. McCarrison left Coonoor before I arrived there and did not attempt to influence the future policy of the Laboratories beyond offering a few words of fatherly advice. His parting words to me in London were: 'Remember: Things move slowly in the East. Good hunting!' But while I did not have the opportunity of working with McCarrison, even for a short period, I found the Laboratories strongly imbued with his personality. Of particular interest was a series of files in which were enshrined acrimonious correspondence with the Government of India about the life and death of the Beri-beri Inquiry, with pointed comments on the obtuseness of officials who failed to understand that nutrition is India's primary problem. These could be read with pleasure during the sleepier hours of the afternoon. They showed that the Nutrition Research Laboratories had not brought themselves into existence. Their creation and 'putting nutrition on the map in India' were the result of a long struggle on the part of McCarrison.

The next stage was to extend the activities and interests of the Laboratories in numerous directions. There was an obvious need for a systematic study of the nutritive value of Indian foods. Towards the end of 1935, two additional research workers (M. Swaminathan and A. S. Sundararajan) were appointed to undertake, in the first place, the ordinary chemical analysis of foods, and within two years the calorie value and the protein, fat, carbohydrate and mineral content of between two and three hundred common Indian foods were determined. Simultaneously the vitamin content of foods was investigated and this became one of the major interests of the Laboratories during the next ten years, an interest not confined to the application of recognized methods. Much pioneer work was done on the establishment of new and improved methods. Of these perhaps the most important was the cyanogen bromide test for niacin described by Swaminathan in 1938 and subsequently adopted and modified in numerous laboratories throughout the world, sometimes without acknowledgement of its original source. The same worker originated in 1940 a chemical test for vitamin B_6 (pyridoxine) which was less widely used by workers elsewhere because more convenient tests for this vitamin were coming into vogue. At a somewhat later stage an astonishingly successful method of testing for vitamins of the B group by the use of rice-moth larvae (*corcyra cephalonica St.*) was devised by P. S. Serma. The titles of numerous papers published between 1935 and 1945 indicate that attention was given to many aspects of food analysis and the testing of foods for nutrients; their subject matter includes the biological value of proteins in common foods, vitamin A and carotene, vitamin C, vitamin D, available iron, phytin phosphorus and oxalic acid. Work on vitamin A had an interesting practical outcome. It was found that samples of shark-liver oil had in general a very high vitamin A content, far exceeding that of cod-liver oil. As a result of this observation and much persuasive activity, a plant for the production of shark-liver oil was established in Calicut in Malabar. Later a similar plant was set up near Bombay city. The somewhat crude preparations of shark-liver oil produced in these centres proved useful during the war when supplies of cod-liver oil from abroad were cut off.

Some knowledge had previously been available about the diets eaten by different communities and groups in India and had been used by McCarrison in his experiments. It was felt, however, that this should be extended and made more quantitative. In 1936 three field workers were appointed to make surveys of diet and state of nutrition, this development being financed by a grant of Rs150,000 from the I.R.F.A. Over a series of years more than a hundred surveys were made in different parts of India; workers on the staff, or workers in Public Health Departments trained in the Laboratories, were responsible for the great majority of these. A useful mass of data, with a direct bearing on agricultural policy, was obtained. It was found, for example, that the diet of the poor rice-eater was essentially the same all over India. He consumed, in addition to his staple cereal, which supplied 80–90 per cent of total calories, only very small quantities of other foods such as pulses, vegetables, fruits and meat; milk and milk products were taken in negligible quantities or not at all. The present Director of the Laboratories, Dr. V. N. Patwardhan, has pointed out that these surveys provide 'a base line against which the results obtained in surveys carried out in post-war years can be evaluated'. The deterioration of the food situation in India may be such that the picture of under- and malnutrition revealed by the earlier surveys must be replaced by a still more gloomy one.

Certain surveys were of special interest. Among these were surveys of manioc-eating groups in south-west India and of a group in an area in north-east Madras in which beri-beri was endemic. K. Mitra, who after training in the Laboratories carried out nutrition work in Bihar, demonstrated striking differences in diet associated with differences in income, repeating on a small scale the investigations of Orr in Great Britain, described in the latter's well-known book, *Food, Health and Income*.

A convenient field of investigation was found in children's hostels and boarding schools supported by missionary societies of various denominations. The children in these institutions were often badly fed, both because money was short and the supervisors lacked knowledge of nutritional principles. The story was told that in one hostel the great majority of children contracted night-blindness and were in danger of being unable to attend evening service after dark. This difficult problem was solved by placing the few children who could see at the head of a long queue of children who clung to the skirt or shirt of the preceding child. A study was made of institutional diets and an attempt made to correlate diet and the incidence of deficiency states such as stomatitis, xerophthalmia and phrynoderma. In some hostels supplementary feeding experiments were done. It was shown that the regular provision of skimmed milk accelerated growth and improved general health. These experiments were the first to demonstrate the value of skimmed milk in the supplementary feeding of children in a tropical country. During recent years the use of skimmed milk in school feeding has been enormously developed by the United Nations International Children's Emergency Fund (UNICEF). A gratifying practical result of the Coonoor experiments was that the Government of India reduced the import duty on skimmed milk powder.

Parallel with human dietary studies and experiments were laboratory experiments in which rats were fed on diets of the human type based on staple foods such as rice, millet and manioc. The result of supplementing these diets in various ways was observed. The effect of adding skimmed milk powder to a poor rice diet was so striking that it was later used for teaching purposes. In a few weeks young rats given the supplement of milk put on more than twice as much weight as animals receiving the poor rice diet alone.

A very definite change for the better later took place in the feeding of children in residential institutions, at least in South India where the influence of the Laboratories was strongest. Those in charge learned to improve and diversify the children's diet without very appreciable increase in cost. The staff of the Laboratories, while gratified at the achievement of a practical result, grumbled because children's homes were no longer museums for the study of malnutrition and deficiency disease.

Rice is the largest crop of the Indian peninsula; in undivided India its production exceeded that of all other cereals put together. Since rice-eaters may obtain as much as 80–90 per cent of their total calories from rice, the nutrient content of rice as consumed is of great importance.

It has long been known that the machine-milling of rice, which removes the germ and the outer layers of the grain, greatly reduces its thiamine content. The epidemiology of beri-beri in rice-eating countries turns to some extent on this fact. The use of home-pounded or under-milled rice, which retains a fair proportion of the thiamine present in the intact grain, in place of highly-milled white rice has been vigorously advocated, though without much success. Parboiled rice and raw (unparboiled) rice behave differently when subjected to milling. The former can be milled to a high degree without serious reduction in thiamine content, because during the steaming which is part of the parboiling process the vitamin changes its position in the grain, passing from the germ and outer layers into the endosperm. The effect of milling on the thiamine content of raw and parboiled rice was systematically studied in the Laboratories during the years 1937–40, and the results were presented in a publication called 'The Rice Problem in India'. R. Passmore, who was Assistant Director during this period, played an important part in these investigations.

The later stages in the preparation of rice for consumption—washing and cooking—were also studied in detail. It was found that the washing of raw rice in the vigorous way customary in many parts of India removes almost entirely what little thiamine is left after milling; subsequent cooking has a less important effect. Parboiled rice, on the other hand, loses much less thiamine when it is washed, since the location of the vitamin in the interior of the grain makes it less accessible to the washing-water.

These facts helped to explain the geographical incidence of beri-beri in India. Beri-beri was found to exist as an important public health problem only in a large area on the east coast in which the people prefer raw to parboiled rice. Later the prevalence of infantile beri-beri in this area was demonstrated by statistical and field investigations and steps were taken to encourage its treatment by injections of thiamine. Infants almost on the point of death from infantile beri-beri or thiamine deficiency can readily be saved by thiamine injections, which take effect in a few hours.

During this period the Nutrition Research Laboratories were not themselves equipped for clinical research. Some studies of deficiency diseases, including therapeutic trials, were however made as opportunity arose. Stomatitis associated with deficiency of members of the B group of vitamins, in particular riboflavin, was described for the first time in India and found to respond to treatment by yeast and skimmed milk. Xerophthalmia and night-blindness occurring in malnourished subjects were studied, particularly in children's homes and famine camps. The effect of treating phrynoderma or toad-skin with vitamin A concentrates was observed and histo-pathological investigations made of this condition and of other skin conditions occurring in malnourished individuals. Work in the field of pathology—of special interest to the Laboratories because it had been a principal interest of their founder—was continued by Radhakrishna Rao. Xerophthalmia, nerve degeneration and skin lesions in vitamin A deficient animals were investigated. A detailed study was made of intestinal changes in monkeys fed on poor rice diets; this was in a sense a continuation of McCarrison's work in the earliest days of the Beri-beri Inquiry.

From 1942 to 1945 a series of clinical investigations were made in hospitals in Madras city. The Government Ophthalmic Hospital in Madras was—and no doubt still is—an institution providing all too abundant material for such research. It was shown that a certain type of superficial keratitis rapidly improves when the patient is given pure riboflavin. An investigation was made of a condition described as 'partial atrophy of the optic nerve associated with vitamin deficiency', which a year or so later affected many prisoners in Japanese camps. The relation between nutrition and diseases of the eye has as yet been insufficiently studied; the World Health Organization has recently drawn attention to the importance of this subject.

A small clinic for the study of deficiency diseases was established in the Stanley Hospital, located in the poorest quarter of Madras. Here it was found that diarrhoea due to nutritional causes is a common complaint among poor Madrassis. The interesting condition 'burning feet', first observed in India early in the nineteenth century and recently familiar to many European doctors in Japanese prison camps, was described in detail and the therapeutic effect of one of the vitamins of the B group—pantothenic acid—demonstrated.

Since India is a country in which malnutrition abounds, it is pleasing to record that its inhabitants are relatively free from one condition for which dietary defects have been held responsible: namely, dental caries.

This fact was elicited by a series of field investigations made by K. L. Shourie in different parts of the country. To say that 'the worse-fed and the poorer the individuals, the better their teeth' sums up the results of Shourie's studies would be an exaggeration, but he certainly found that the incidence of dental caries rose with increasing income, and that the Anglo-Indians were the only community exhibiting caries in any marked degree. The Anglo-Indians, though in general miserably poor, were better off than the mass of the Indian population. Their susceptibility to caries seemed to be related to their diet, which was often the 'poor European type', containing large quantities of white bread and a good deal of sugar.

It was also shown that, in India as elsewhere in the world, there is an inverse relation between dental caries and fluorosis. Another part of Shourie's work was concerned with the scorbutic-like lesions of the gums which are particularly common in north India and are not affected by treatment with vitamin C.

In planning 'Nutrition Research' in 1927, McCarrison included education among its activities. He commented that the Coonoor unit had come to be regarded by official and private bodies and by the public generally as a central information bureau. Year by year the demand for information increased and the need for educational work became more and more evident. One way of meeting the need was the preparation of popular books, bulletins, pamphlets and posters. The success of McCarrison's little book *Food* has already been mentioned. During the years 1935–45 a number of popular bulletins were issued in the Government of India 'Health Bulletin' series. One of these, 'Health Bulletin No. 23, The Nutritive Value of Indian Foods and the Planning of Satisfactory Diets', provided information, in simple language, about the general principles of nutrition and 'well-balanced diets' and included tables showing the calorie and nutrient content of Indian foods, based on work done in the Laboratories. Health Bulletin No. 23, which cost only two annas, proved a best-seller; within ten years three editions appeared and each edition was reprinted several times. A new edition, further revised, was issued in 1951. The bulletin was translated into several Indian languages. Another bulletin, called 'Rice', presented facts about the nutritive value of rice and rice diets in popular form; and a third, intended for use in schools, gave a simplified account of nutrition and its importance in India.

A museum containing photographs, charts and exhibits, some from McCarrison's collection, was set up in a large room in the Pasteur Institute. These were presented so as to be as far as possible self-explanatory. The visitors who flocked to the Laboratories, particularly during the holiday season, were taken round the museum and shown a selection of its material. It proved invaluable for this purpose and enabled the staff to deal with visitors ranging from governors, maharajas and members of the Congress Party to groups of local school children. Uninstructed visitors to scientific institutions become frustrated when taken from laboratory to laboratory to peer at incomprehensible apparatus. It was the custom of the Laboratories to keep open house to visitors of all kinds, though at times one felt that a less hospitable attitude would have been fully justified.

Since 1937 nutrition courses lasting eight to twelve weeks have been given every year in the Laboratories (except in 1946). These have been attended by officers in public health departments, medical and scientific graduates, health visitors, social workers, missionaries, teachers and others to whom knowledge of nutrition is useful in the execution of their ordinary duties and who can pass on knowledge to the people. Some of the provincial public health officers attending the course subsequently did most useful work in provincial health departments. As part of their training, the students did simple dietary experiments with rats, guinea-pigs and pigeons. Demonstrations on the part of the staff included the dramatic cure of thiamine-deficient pigeons with head retraction; given an injection of 1 mg. of thiamine the affected birds invariably recovered within ten minutes before the eyes of the class. The highly-milled rice fed to the pigeons was washed with extreme vigour to ensure the rapid development of thiamine deficiency.

During the war the advisory work of the Laboratories greatly increased. The newly created Department of Food sought advice on many subjects, including food technology. The army authorities also made considerable use of the services offered by the Laboratories, among which was the determination of the vitamin content of foods issued to the army. Military associations were strengthened when the author was appointed 'Honorary Consultant in Nutrition' to the army in 1943.

Mention should be made of the Nutrition Advisory Committee of the Indian Research Fund Association (now the Indian Council for Medical Research), with which the Laboratories have been closely associated. The Nutrition Advisory Committee met first in 1936 and has met once, twice and occasionally three times a year ever since. The Director of the Nutrition Research Laboratories has been its secretary throughout. The original purpose of the N.A.C. was to advise the I.R.F.A. about the allocation of funds for nutrition research; it still retains this function. But as time went on the Committee assumed many other functions. It has made pronouncements and advised the Government on food and agricultural policy and on the nutritional needs of the population. It has considered special problems such as the nutritive value of hydrogenated vegetable oils (space would not permit reference here to the great animal-versus-vegetable-ghee controversy which still rages in India) and the introduction of soya bean into the Indian dietary. Sometimes it has arranged for co-ordinated experiments, designed to throw light on some specific question, to be done simultaneously in a number of different laboratories. Apart from its advisory functions, the Nutrition Advisory Committee has been of value as a link between nutrition workers in different parts of India, separated by long distances and with relatively rare opportunities of meeting each other. Since its membership has included representatives of the agriculture, food and other departments, it has also served as a link between nutrition workers and workers in associated fields and has done a good deal to make the latter aware of nutritional ideas and principles.

The Nutrition Research Laboratories have throughout their existence been financed by the Indian Research Fund Associations and its successor, the Indian Council for Medical Research. Until recently the Public Health Commissioner with the Government of India was ex-officio secretary of the I.R.F.A. In the early days of the research unit there were, as has been recorded, some sharp struggles between McCarrison and the authorities concerned with financing research. But lack of enthusiasm for nutrition research was soon replaced by a co-operative attitude consequent upon the Report of the Linlithgow Commission in 1930. Therefore, during the latter part of McCarrison's term as Director and during my term help and friendly encouragement were received from the I.R.F.A. Secretaries. They smoothed over administrative difficulties and were always ready at least to listen to the requests for additional funds with which all research workers torment governing bodies and administrative chiefs.

The present Director of the Laboratories, Dr. V. N. Patwardhan, who took charge in 1946, comes from Poona in the Bombay Presidency (now State). He belongs to the Mahratta people who in the early years of the nineteenth century struggled fiercely with the British for the possession of western India and who during the disintegration of the Mogul Empire imposed overlordship on a number of Central Indian states. Patwardhan had previously been Professor of Biochemistry in the G. Seth Medical College in Bombay. He had done valuable research on a variety of nutritional problems and had for a number of years been keenly interested in broad questions of food and nutrition policy in India. He has throughout played an important part in the work of the Nutrition Advisory Committee.

The Nutrition Research Laboratories, Coonoor

The research programme of the Laboratories, as described in Annual Reports from 1946 onwards, covers a wide range of subjects. The analysis of Indian foods has been continued, accompanied by research on methods of analysis. A series of investigations have been made on the physiological action and metabolism of various vitamins, including vitamin A and carotene, riboflavin and panthothenic acid. The excretion of riboflavin by human beings given test doses of this vitamin has been determined. Human volunteers were used for the study of nitrogen balance on poor rice diets and of the nutritive value of hydrogenated oils. Experimental work on human beings of this nature is for practical purposes a new departure in the Laboratories.

G. Gopalan—now Deputy Director of the Laboratories—showed in 1945 that the 'burning feet' syndrome could be relieved by the administration of panthothenic acid. Workers in the U.S.A. found that in panthothenic-acid-deficient rats capacity to acetylate para-amino-benzoic acid is reduced. The same phenomenon was found to occur in human beings with 'burning feet'—supporting evidence that this condition is associated with panthothenic-acid deficiency.

Surveys of diet and state of nutrition have been continued. A survey of families working on plantations in south India revealed that the condition of both adults was less satisfactory than in the pre-war period. A schedule for assessing state of nutrition, adopted by the Nutrition Advisory Committee, has been used by the Coonoor staff and by workers elsewhere in the country. To keep a watch on the food situation and its effects on health is an important responsibility of nutrition workers in India.

Mention has been made of the small clinic set up in the Stanley Hospital, Madras, for the study of deficiency diseases. This has been replaced by a Nutrition Clinic in Coonoor itself, where the resources of the Laboratories are available for the clinic. In the new clinic further studies have been made of nutritional diarrhoea and phrynoderma; other investigations have been concerned with nutritional oedema and its pathogenesis, round-worm infestation and deficiency disease and nutritional macrocytic anaemia. Of particular interest is research on the syndrome associated with protein deficiency and known by a variety of names including 'kwashiorkor' and 'malignant malnutrition'. It has been found that a condition closely resembling kwashiorkor as described in East and South Africa occurs in India. As in Africa, cases have been successfully treated by skimmed milk. Fatty degeneration of the liver is among the characteristic signs of the kwashiorkor syndrome. Experiments recently reported from Coonoor, in which attempts were made to produce liver changes in rats by feeding them on poor rice diets and the role of methionine on the lipotrophic function of the liver was studied, have a bearing on this important problem.

There are reports of further work on two conditions in which McCarrison was interested in the earlier days of the Laboratories: stone in the bladder and lathyrism. The aetiology of the latter—as it occurs in India—remains obscure. As far as epidemiology is concerned, lathyrism presents a clear picture, but attempts to reproduce the disease in animals in the Coonoor and other laboratories have on the whole been singularly unsuccessful. Other interests of the Nutrition Research Laboratories during recent years, to which bare reference may be made, are the establishment of haematological standards, the nutritive value of soya bean and the digestibility and metabolism of hydrogenated vegetable oils in human subjects. Investigations on hydrogenated oils have formed part of a co-ordinated investigation undertaken in five laboratories in India under the auspices of the Government.

The staff establishment as shown in the Annual Report for 1949–50 included some twenty posts for scientifically qualified workers. In addition to two Parlakimedi Research Scholars, there were an Apostolos Raptakos Research Scholar, a University of Travancore Research Scholar and a Lady Tata Memorial Scholar. In 1940 there were fourteen research workers on the staff; in 1930 not more than three, including McCarrison. The important position of the Laboratories in the field of nutrition research is recognized outside India. For example, the Director was elected chairman of the FAO Regional Nutrition Committee for South and East Asia (1948) and is a member of the Joint FAO/WHO Advisory Committee on Nutrition.

Enormous political changes have taken place in India during the brief lifetime—1918 to 1951—of the Nutrition Research Laboratories. These are reflected in the history of this institution as in that of every other institution in India. For example, until the partition of India in 1946, the Laboratories served the whole Indian peninsula. Largely because of their location in the far south, they were on the whole more concerned with the problems of what is now India than with those of what is now Pakistan. But there were numerous associations with the areas which now are outside the jurisdiction of the Government of India. The field studies of the Laboratories, as well as their advisory services, extended into these areas and workers from the North-West Provinces attended the nutrition courses. These associations have now been largely severed.

The Laboratories during their brief history have shared in the process which culminated in Indian independence. When the Beri-beri Inquiry was instituted in 1918, there were no qualified Indian nutritional research workers; McCarrison worked with assistants whom he himself trained. From 1919 to 1926, twenty-seven papers were published from the Laboratories; of these, twenty-five bear the name of McCarrison alone, since he was the only qualified research worker, and two the names of other British workers in addition to McCarrison's. An Indian name first appears on a publication in 1927, one of four of which three were British. From 1930 to 1935 there are more Indian names in the publication list. Out of 167 publications of various kinds issued between 1935 and 1945 more than 80 per cent bear the signature of Indian workers alone.

In 1935 the appointment of a European Director as successor to McCarrison was accepted almost without question; no Indian worker suitably qualified for the post was available at that time. In 1946 there was equally no question of appointing a Director other than an Indian. Thus, step by step, McCarrison's creation has become an Indian institution. Enough has been said to show that it is to-day an active and vigorous institution.

The history of the Laboratories must also be set against another background—more important than the political. During the first forty years or so of the present century, what is nowadays called the 'food situation' gave rise to little anxiety in India. After a serious famine at the turn of the century, only minor famines occurred which were easily controlled and limited. Agricultural science was successful in increasing the production of certain crops, notably cotton and sugar. The monumental Report of the Royal Commission on Agriculture in India (1930), while it recognizes the formidable difficulties to be overcome in developing agriculture, is on the whole a hopeful document. McCarrison preached from the text 'Eat ye that which is good' in an optimistic spirit, and up to 1943 there appeared to be some justification for this attitude. Then came the terrible Bengal Famine, to be followed by a period of food shortage to which no end is yet in sight. Partition, which cut off India from a number of 'surplus' food-producing areas, made things worse and during recent years food production has been hampered by a series of natural calamities. It is only by drastic food control and rationing that many millions have been and are kept from starvation. The food situation in India and elsewhere in East Asia is coming to be thought of as a grim race between agricultural development and population growth. There is an anxious obsession with the question of food supply which did not exist twenty years ago.

The main objective of an institution devoted to human nutrition research is to find ways and means of improving human diets. If circumstances make such improvement impossible (except here and there and on a very limited scale), people tend to ask the nutrition research worker: 'What is the good of all this? Is it helping to feed the people?' They may add: 'What the country needs is more food and not nutrition research.' There are valid answers to such questions. In fact it is not difficult to show that there is more need for nutrition research and knowledge of nutrition when food is scarce than when it is abundant. This point need not be further pursued here. It is sufficient to emphasize that the environment of an institution devoted to nutrition research in India is very different from that of a similar institution in, let us say, Iowa, and cannot be without profound influence on its history and future development. As far as the food situation in India is concerned, there is at least a reasonable prospect that rearguard action may give place to steady advance as efforts to apply scientific methods of agricultural production come to fruition. The menace of increasing population pressure may diminish with a rise in living standards and a change in social attitudes. In such circumstances it will be possible to apply effectively and on a wide scale the results of many years of nutrition research.

It will be evident—at least to some readers—that this historical survey has not been written in a critical spirit. I am aware that some of McCarrison's laboratory research and his interpretation of its results have been criticized and even more aware of the defects of some of the work done during the period of my own directorship. Mistakes and failings have been left out of the record. The best excuse is that time has the same effect. After an interval of fifteen to twenty years the value of McCarrison's contribution to the science of nutrition is abundantly evident and little importance need be attached to the occasional errors of an enthusiastic pioneer exploring new territory.

PROLOGUE

2. Sir Robert McCarrison's Place in the History of Nutritional Research

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In retrospect the situation concerning knowledge of nutrition in 1914, the year in which McCarrison first discussed his experimental studies on the aetiology of endemic cretinism, congenital goitre and congenital parathyroid disease, may be briefly stated somewhat as follows.

The work of Kossel, E. Fischer, Abderhalden, Osborne and others, had revealed that great differences in the amino-acid composition of proteins from different sources must be interpreted to mean that corresponding differences in their nutritive values would be demonstrable by experiment. Osborne and Mendel, between 1911 and 1916, using their 'protein-free milk' and isolated protein formulas, had dramatized the significance of individual amino-acid deficiency in animal nutrition. Diets deficient in lysine or tryptophan, for example, caused profound malnutrition in rats. The protein moiety in nutrition assumed great prominence in considerations of the relation of diet to health.

The great discovery of Eijkman in 1896, that polyneuritis in fowls results from restricting them to a diet of polished rice, initiated the studies of Vordermann, Grijns, Hulshoff-Pol, Fraser and Stanton, Fletcher, and others, to epoch-making discoveries which clearly demonstrated that beri-beri in man is a deficiency disease, in its uncomplicated form, by deficiency in the diet of a basic substance of which but a minute amount was required, with an otherwise adequate diet, to sustain normal health. This astonishing discovery, foreshadowed in the experimental results of Lunin, Pekelharing and Hopkins, aroused greater interest in nutritional investigations than had hitherto prevailed.

Von Bunge, in the 1870s, had opened a new field of nutritional investigations by his prophetic discussions of the significance of acid-base balance in physiology, and of the influence of the ingestion of one inorganic element on the excretion of another. Thenceforth the inorganic portion of 'ash constituents' were to receive increasing attention, although intensive work in this field was to be delayed until after 1900. The studies of Ringer on the 'physiological' salt solution and of J. Loeb on the metabolic disturbances which arise as a result of 'unbalanced' salt solutions, aroused great expectations for research on the effects of various inorganic ions in physiological processes, which later studies have fully justified.

Between 1895 and 1910 the question whether the animal body is capable of synthesizing the organic phosphorus compounds—nucleic acids, phosphoproteins, lecithins, kephalins, etc.—was prominent in the thoughts of those who sought to nourish young animals on diets consisting of isolated and purified nutrients recombined in what appeared to be suitable proportions. This question was answered by McCollum and his associates by the demonstration that all types of organic phosphorus compounds found in the animal body can arise from synthesis, and that the phosphorus in the orthophosphate ion can serve for all of these syntheses. Plimmer came to the same conclusion (1909, 1913) on the basis of evidence that in the processes of digestion and assimilation all these organic phosphoric compounds are hydrolized into phosphate and the organic moiety, so that no matter what form of phosphorus compounds are ingested as food the end result is that the body deals with the cleavage products rather than the substances eaten. Thenceforth deficiency of any organic phosphorus compound was ruled out of consideration as a cause of any type of malnutrition which might arise.

All efforts to keep in health animals restricted to the diets of 'purified' food substances were, up to 1910, either total failures or attended by but little success. Such successes as were realized involved the significance of coprophagy and of unsuspected impurities in the food ingredients, both of these defects in experiments being sources of indispensable nutrients now known as sources of vitamins, could not at that time be evaluated. One important discovery came from this type of experiment, however. In 1913 McCollum and Davis described their demonstration of pronounced difference in nutritive value between butter fat and egg-yolk fats (ether-soluble material) on the one hand, and lard and olive oil on the other. The substance responsible for this difference withstood saponification, and was transferred from soaps made from butter fat to olive oil. This, the first of the fat-soluble vitamins to be discovered, made possible a new kind of experimental study of the nature of the deficiencies of individual cereal grains. Thus McCollum and Davis

(1913–14) showed that the wheat, maize and oat kernel resemble each other in that they require the same three additions of known substances to render them essentially complete as the source of food for a young animal. These additions are a source of vitamin A, calcium, and certain amino-acids (especially lysine and tryptophan). No one and no two of these will supplement one of these grains so as to make it support good growth in young rats.

It should be again emphasized that we are discussing the state of knowledge in 1915 in retrospect, and that there still was marked difference of belief among the best-informed experimenters. Thus Funk in 1915 still asserted that polished rice, supplemented with the anti-beri-beri vitamin, was a complete food for a pigeon. He and Macallum vigorously controverted the statements of McCollum and Davis concerning the existence of a vitamin in fats. Forbes, in the same year, still interpreted certain experiments with swine to mean that organic forms of phosphorus were necessary in the food, and their absence or restriction resulted in inferiority of the animals. There was no general acceptance among nutritional investigators of the idea that what are now known as vitamins play an important role in the human or animal diet. The study of McCollum and Davis, in 1915, showed that for young rats polished rice is not made complete nutritionally by the three simple additions which are highly effective in making good the deficiencies of *whole* cereal grains, but requires a fourth supplement which carries a water-soluble something (later shown to be a mixture of a number of vitamins). This could be obtained from almost any entire natural food. It was, accordingly, postulated that in addition to the long recognized 'staminal principles' of Prout and Mulder, two types of unidentified substances are necessary for normal nutrition, neither of which food analysts knew how to test for or to estimate.

In the 1890s, in the U.S.A., a human experiment on a nation-wide scale was in progress. It related to scurvy in infants. The American physicians had become convinced of the danger attending the feeding of infants on raw milk formulae, because of the repeated demonstration that milk could be a transmitter of several diseases, such as typhoid fever, scarlet fever, septic sore throat and bovine tuberculosis. They at that time followed the leadership of certain German paediatricians who recommended boiled milk formulae supplemented with barley water. On this regimen infants brought up on the bottle suffered from scurvy. City after city adopted an ordinance requiring the pasteurization of market milk, which accomplished much in increasing the incidence of scurvy in infants.

In 1912 Holst and Frölich, in Oslo, showed conclusively that guinea-pigs fed dry or cooked food developed scorbutic lesions, whereas the same articles (e.g. dandelion greens), if fed raw, would prevent or cure scurvy in these animals. It was this study which induced A. F. Hess of New York (1915) to substitute potato water for barley water in infant feeding and to demonstrate its effectiveness as an antiscorbutic. He then quickly induced the general adoption of the practice of providing raw fruit or vegetable juice to artificially fed infants, and so almost eradicated scurvy among the infant population.

But all these discoveries which were of record in 1915 were not yet matured in the public mind, and so, while at that time it was actually possible to produce uncomplicated single nutrient deficiency states involving (a) the antiscorbutic factor, (b) lysine, (c) tryptophan, (d) vitamin A, there yet remained so many unsuspected nutrients to be discovered that in making an inquiry into the effects of human diets restricted to a few articles, and so constituted as to induce borderline malnutritional states as respects several nutrients, could not be utilized in a clear-cut experimental procedure. In 1914 Goldberger expressed his belief, based on shrewd observations, that pellagra was a deficiency disease, but in the same year the Thompson-McFadden Commission asserted that it was a transmissable disease carried by the stable fly. The aetiology of rickets was quite unknown. The merits of high protein versus low protein consumption had been discussed at length, Chittenden defending abstemiousness in protein consumption, with Sir James Crichton-Browne, D. McCay and F. G. Benedict opposing him. None of these careful observers and critical thinkers comprehended the complexity of the problem of nutrition they were debating.

In the second edition of *The Vitamins* (1922), Funk stated: 'Till recently everyone was of the opinion that in avian beri-beri the manifestations in the central nervous system were in the foreground. The new investigations show, on the other hand, that as a result of lack of vitamin B many, if not all, of the organs suffer, and for this reason the disease cannot be thought of as "polyneuritis". Despite many attempts, it has not yet been possible to find which organ or tissue is primarily responsible for the manifestations of the disease. This is, of course, bound up with our insufficient knowledge of the physiology and significance of the vitamins.' Funk might well have extended his list beyond the vitamins, to include amino-acids and inorganic substances at the time he wrote the paragraph just quoted, for in 1922 these were well-established dietary essentials.

Descriptive of the state of knowledge of malnutrition was the statement of McCarrison in his paper on *The Pathogenesis of Deficiency Disease* (1919): 'The influence of "vitaminic" deficiency on the adrenal glands, on the pancreas, on the liver, and the spleen, is, so far as I can ascertain from available literature, unknown; while that of the thyroid apparatus has been but incompletely studied. Nor are we better informed with respect to the other important structures of the body as, for example, the pituitary gland and the reproductive organs.' He said that he was attempting to fill in some of the gaps in our knowledge.

The situation as respects knowledge of malnutrition at that time may be further illustrated by the fact that everyone who had had experience with the production of what was termed 'polyneuritis' in pigeons by restricting them to a diet of polished rice had observed that after a few days the birds cease to eat, and if forcibly fed the crop became obstructed with a hard mass of swollen and adherent rice grains, and this crop-stasis resulted in complete or nearly complete inanition. No one was in a position to decide how far the symptoms of the birds was the result of fasting and how far of lack of a specific chemical substance, the 'vitamine' of Funk, deficiency of which was believed to be the aetiological factor in producing the disease. McCarrison called attention to the confusion which arose out of failure to distinguish between the effects of inanition and deprivation of vitamins.

McCarrison in his investigations broadened the study of beri-beri to include more than the concept that the disease is essentially the result of nerve injury. He sought to examine carefully the histological and functional changes and the sequence of events in inanition as a preliminary to interpreting the phenomena of physiologic failure on incomplete diets; and he did all that could be done at that time to plan his diets so as to make the deficiency states which resulted from their use as nearly as might be the result of lack of a single chemical substance. At the time when he entered upon his great programme of study it was not possible to succeed very far in accomplishing this objective. His work was planned much more comprehensively than any other study which antedated or was contemporaneous with his.

It will add something to the historical perspective in which we should view the researches of McCarrison to point out that although many isolated observations had from antiquity been recorded on the effects of inanition on the anatomical and physiological status of human beings, there were so many gaps in knowledge in this field that Jackson, writing on the subject in 1929, cited over six hundred communications to be found in scientific literature, and almost all of these were dated after the year 1920. McCarrison's earlier investigations, in which he distinguished between total inanition, partial inanition, and specific starvation for individual nutrients, were available to the numerous students in this field during the 1920s.

McCarrison's statement made in 1919, 'The want of substances essential for the normal metabolism of the human and animal body suggests the need for examining the effects of their deficiency on the organs responsible for digestion and assimilation, and for the regulation of the metabolic processes,' proved prophetic. Knowledge in this field, he pointed out, was very scanty. What he did served to an important degree to orient the thinking of investigators whose horizons were narrower than his, and to teach how comprehensive must be investigations in nutrition if the subject were to be adequately understood. As in other fields of scientific inquiry, nutritional research suffered from workers who contributed too much logic based on too little observation; and from others who contributed a plethora of observations made without benefit of logic. There was much in McCarrison's writings and lectures which raised the standards of students of pathology and of normal nutrition of those who followed after him.

Sir Robert possesses in enviable measure qualities which are admirable in the eyes of his many friends and admirers. Intellectual honesty, enthusiasm, curiosity, studious attention to interpreting his observations in the full light of the work of others, courage of conviction in unusual measure in defending his considered conclusions are characteristic of him. He possessed not only knowledge but wisdom.

The writer cannot forbear ending this account on a personal note, by mentioning his genial disposition, fine sense of humour, obvious interest in people, and charm in conversation which made for him a host of friends and admirers in many lands. It is a pleasure to one who marched with him through two decades toward the distant watch-fires of truth to express high regard for him as a man as well as an invesigator.

PROLOGUE

3. The Present Importance of Sir Robert McCarrison's Work

I. STUDIES ON FAULTY DIETS

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INTRODUCTION

Medicine is a blend of a practical art, a theoretical science and an applied science. The art is handed down from master to apprentice according to traditional rules, and is very gradually improved by the intuition and skill of individual artists. The applied science depends upon the theoretical science, and this is advanced in two different ways by the use of the experimental method. The first may be broadly called Experimental Physiology and the second Clinical Science. The experimental physiologist—whether he works in a laboratory called physiological, biochemical, pathological, pharmacological, nutritional, or given one of a number of other descriptions—is concerned with advancing knowledge of the fundamental processes of organisms conveniently called 'living'; he is not essentially concerned with advancing the applied science of medicine, although his discoveries may well have a profound effect upon the prevention or treatment of disease in man. The clinical scientist uses the experimental method upon man and lower animals to elucidate disease. There is no difference of method and little difference of material, but there is a difference of inspiration and aim: the clinical scientist starts with the sick patient, and then studies living men in health or disease, or dead men, or lower animals, perhaps making his experimental studies in one of the laboratories already mentioned; the experimental physiologist starts with a basic problem which he then tackles in a similar way. In either case the method of experimentation is almost exclusively used; the alternative method of pure observation, as Trotter so well emphasized, is very limited as an instrument of inquiry and is especially open to the *post hoc* fallacy. This is not to belittle the value of observing phenomena that occur in different regions of the world 'where nature makes large-scale experiments upon man' (McCarrison), for such experiments may not be justifiable in the laboratory. India is such a region.

Sir Charles Sherrington, when in his nineties, told me that when he finished working with Koch in Berlin, he went to thank him and seek his advice about the future. Koch, 'our medical Galileo, who . . . introduced us to a new world' (Osler), advised Sherrington to join the Indian Medical Service since he believed that the greatest advances in medicine would be made by studying the diseases endemic in that country. Sherrington returned to England fired with enthusiasm to follow this advice but, being just over thirty, found (erroneously) that he was too old. Fourteen years later McCarrison, who subsequently worked in Sherrington's Laboratory in Oxford, joined the Indian Medical Service and sailed for India.

'THREE-DAY FEVER'

At his first station he met and investigated an apparently new disease, the 'Three-day Fever of Chitral' (see p. 2). After careful observations he became convinced that it was transmitted by the sand-fly, but with the primitive facilities available he was unable to prove either the infectivity of the blood or the role of the sand-fly as vector; and then he was posted elsewhere. It remained for Doerr (1908) to prove that the three-day fever was caused by a virus transmitted by the sand-fly (*Phlebotomus*) five years after McCarrison's work. As McCarrison indicates in the first chapter of this book, the experience was valuable for him in teaching him to observe carefully and to experiment even without, or with but few. laboratory aids to research. At the same time he began his studies on goitre and cretinism, which are the subject of the second chapter and of Mr. Selwyn Taylor's assessment at the end of this section. Claude Bernard in his *Physiologie Opératoire* (1879) had stated that absolutely nothing was known of the function of the thyroid and adrenal glands. Though the subsequent work of Horsley, Schiff, Murray, Schäfer and others rapidly provided information about the thyroid, knowledge was still meagre at the turn of the century.

EARLY DIFFICULTIES IN COONOOR

McCarrison's study of the thyroid gland and its disorders included the effects of deficient food upon this organ, and hence he was led in

1914 to begin a wider series of researches into the nature of deficiency diseases. In the summer of 1913 a fine Sikh, Sub-Assistant Surgeon Mula Singh, had joined him but in October 1914 they both went on active service. Those researches were resumed upon his return to India in 1918. Little nutritional work had been done in India; the limited facilities for research were largely being used for the study of infectious diseases. Famines were more common than in any other part of the world; Loveday in his *The History and Economics of Indian Famines* (1914) wrote: 'It would probably be possible to find proof of local failure of crops, and ensuing distress, in some part of India in every year of the last two centuries'. An unprecedented famine had occurred in 1899–1900, yet almost no scientific observations were made. An exception was the work of Porter who had investigated oedema in famine and also published in 1889 a study of *The Diseases of the Madras Famine of 1877–8*. Occasional papers were produced on epidemic dropsy, such as McLeod's study in Calcutta (1881). A little work had been done on beri-beri of which the most important was Malcolmson's *A Practical Essay on the History and Treatment of Beri-beri* (1835); but this disease was common in only a limited area of the north-east of the Madras Presidency.

Malcolmson was one of the great figures of the Indian Medical Service, and another significant contribution from this service was the publication in 1912 of McCay's *The Protein Element in Nutrition*. Chittenden had recently published his *Physiological Economy in Nutrition* (1905) and *The Nutrition of Man* (1907) in which, as well as in various papers, he had advocated the merits of a diet low in protein. McCay contested this work; from his study of the habits and physique of various races in India and his investigation of prison dietaries, he concluded that a diet high in protein during the period of growth was necessary for the production of an active and virile race of men. This work supported the ideas McCarrison was forming and strengthened his conviction of the importance of studying the effects of deficient and ill-balanced foods on the various organs of the body. He purposely chose a technique different from that being used by others: several biochemists—such as Eijkman, Holst and Frölich, Hopkins, McCollum, Chick, Mellanby, Drummond, Evans, and Goldberger, with their colleagues—were very successfully studying the nutrition of lower animals maintained on simplified diets, thereby defining the nutrients essential in the diet and producing simple deficiencies analogous to scurvy, beri-beri, rickets and pellagra. McCarrison realized that though a single deficiency was primarily responsible for these diseases, other nutrients were likely to be deficient as well; and less-marked deficiencies, alone or in combination, might be responsible for pathological changes and hence ill-health without the production of a specific deficiency disease. Therefore: 'My own method, on the other hand, has been to observe the more general symptomatic and pathological effects of faulty food on the animal body as a whole, and thereby to ascertain what forms of human illness might reasonably be attributed to it.'

It is true and commendable that great work can be done under adverse conditions with apparatus now regarded as primitive: Claude Bernard worked successively in two sheds and a mezzanine room equipped by himself before moving to a 'dark damp tannery', and was forsaken by his wife because he could not afford a carriage. Some scientists have stepped straight into chromium-plated laboratories, filled with electronic apparatus tended by skilled technicians and graced by secretaries who record their sagacity. Other scientists have enthusiastically accepted an empty room which they keep clean themselves while they fight for funds to finance their research. The former are apt to judge the work of the latter without allowance for the conditions and facilities available. When he returned to India in March of 1918, McCarrison acquired an empty room in the Pasteur Institute at Coonoor; on a table he mounted his apparatus—a microscope and a Cambridge rocker microtome. He borrowed a clerk from the post-office through the good services of the Postmaster-General, and his wife, as always, assisted his work and allowed her cook to be used. In July 1918 Mula Singh returned from active service (with the Indian Order of Merit for gallantry) and the cook returned to culinary pursuits. In January 1920 McCarrison was invalided to England for a year and thereafter was seconded for special duty; he studied the relation of dietary fat to the thyroid in Sherrington's Laboratory in Oxford and was joined by Mula Singh who received further training in histological methods in the Department of Zoology. When they returned to Coonoor in 1922 the equipment he had gathered together had been dispersed; he was back to the empty room. Though he succeeded in getting another Sub-Assistant Surgeon appointed—B. G. Krishnan, who had never been in a laboratory before—the Inchcape Committee stopped his work the following year for reasons of economy, and he resigned. In 1925 he returned, and for the third time occupied the empty room, with Mula Singh and Krishnan as his helpers (later the former received the high title Sirdar Bahadur and the latter became Rai-Sahib). His persistence and Irish powers of persuasion stood him in good stead, and soon he acquired and trained technicians and animal attendants. The following year conditions suddenly changed. As Dr. Aykroyd has written earlier in this book (and I need make no apology for repeating facts that are pertinent to his history of the Coonoor Laboratories and to an appraisal of McCarrison's work), the Royal Commission on Agriculture under Lord Linlithgow visited Coonoor in 1926. The chairman mentioned informally that the Madras Presidency put forward more impressive evidence than that of any other Province; the written evidence was three memoranda, on nutrition by McCarrison, on public health by Sir Alexander Russell, and on medical problems by Surgeon-General Hutchison. McCarrison's work deeply impressed Lord Linlithgow, and as he reached the age of fifty the days of the empty room were over.

PATHOGENESIS OF DEFICIENCY DISEASE

In this disjointed period McCarrison had officially been working for the Beri-beri Inquiry. His work was, in fact, wider in its scope, and was published in a series of papers entitled 'The pathogenesis of deficiency disease'; part of this work is included in the third chapter of this book.

To us now his most interesting discovery is probably the hypertrophy of the adrenals in various forms of malnutriture and in undernourishment. The earlier work had been conflicting: Chossat (1843), for instance, found that the adrenals of 3 fasting pigeons which lost 40 per cent of body-weight decreased by more than half as compared with 2 controls; but Manassein's (1868, 1869) 47 fasting adult rabbits, which lost about the same proportion of body-weight, had heavier adrenals than had controls, and this change was the more marked the younger the rabbits. McCarrison found that the adrenals of pigeons that had lost about 40 per cent of body-weight were nearly doubled in weight, and the amount of adrenaline in the glands was increased as judged by physiological and chemical assays. This gain in weight was confirmed by Vincent and Hollenberg (1920, 1921). McCarrison further found that whereas scorbutic guinea-pigs had enlarged adrenals with a decreased content of adrenaline, a diet of autoclaved rice produced in pigeons greatly enlarged adrenals with an increased content of adrenaline. The 'series of important papers' containing this 'very striking result' stimulated the late Sir Charles Kellaway to repeat McCarrison's work which he confirmed (Kellaway, 1920); Korenchevsky (1923) also confirmed the enlargement of the glands in avian beri-beri. McCarrison further found a relationship between the hypertrophy of the adrenals and the occurrence of hydropericardia in his pigeons, and he regarded the excess of fluid as the equivalent of wet beri-beri in man. This work has received insufficient attention, possibly because an hypothesis was developed to explain oedema on the basis of excessive production of adrenaline; this hypothesis was later discarded, and it is probable that the release of adrenaline from the gland is decreased.

The causes of famine oedema and of the oedema of wet beri-beri remain obscure. Many observations have been made in the field during and after World War II, and oedema has occurred in the laboratory in volunteers on diets low in calories (Keys, *et al.*, 1950). Certain authors (Keys, *et al.*, 1946; McCance, 1951, 1952) have explained famine oedema on the basis mainly of loss of weight and consequent decreased tissue tension, but I have criticized this view (Sinclair, 1953) and suggested (Sinclair, 1948) that the hypertrophy of the adrenal cortex may indicate an increased secretion of mineralotropic hormone and retention of sodium and water. Though much more experimental work needs to be done, there may well be truth in McCarrison's early statement that 'In the presence of a diet deficient in vitamin A and B, in protein, and excessively rich in starch, oedema-production is associated with derangement of adrenal function both as to its cortex and as to its medulla.' Nutritional oedema would now generally be associated with the two states McCarrison particularly studied, diets low in calories and those low in thiamine; and most workers would ignore (not necessarily correctly) the adrenal medulla in this context.

BERI-BERI

Although this disease has been known for more than three centuries, certain facts about it are still obscure. In adults the common forms are 'wet' or 'dry'; there is also an acute cardiac beri-beri and a rare convulsive form; intermediate types are of course frequent. McCarrison investigated the aetiology of the different forms by a careful study of the relation of rice to the disease in man and of the production of pathological changes in pigeons on rice diets.

In 1918, when his studies were resumed, it was generally agreed that 'water-soluble B' and 'the anti-neuritic vitamine' were identical. But the different forms of beri-beri and certain anomalies about its occurrence on various diets raised difficulties. A variety of authors believed the aetiology was infective and isolated various forms of micro-organisms from the blood of patients (e.g. Pekelharing and Winkler, 1893; Hunter, 1898); others claimed to have produced beri-beri in lower animals by injecting cultures or toxins of micro-organisms from the blood of human cases (e.g. De Lacerda, 1887; Ogata, 1885; Bernard, 1926); others supported the infective hypothesis by epidemiological studies (e.g. Matsumura, *et al.*, 1929). Both Hamilton Wright (1905) and Sir Arthur Hurst (1917) believed their cases of beri-beri were caused by 'a specific infection of the duodenum, the toxins produced having a specific action on the nervous system'. For two reasons McCarrison might well have been predisposed towards this aetiology: first, he had failed to prove the infectivity of the blood in sand-fly fever, although this was later demonstrated; secondly, in the course of his work on the effect of deficient diets on the endocrine glands he had found organisms resembling *Bacillus suipestifer* in the blood and tissues of polyneuritic pigeons and had produced polyneuritis in two-thirds of animals injected with cultures. Although he stated 'the possibility that there may be an infectious or toxic, as well as dietetic, element' in the causation of 'beri-beri-like maladies', he correctly concluded from his studies that true beri-beri was caused neither by an infection nor by a toxin produced by a micro-organism.

The question of other toxins was more difficult. Spoiled or diseased rice was frequently incriminated: 'My belief is that beri-beri is due to some peculiar fungus growing in the rice kept in damp godowns for a long time' (Mukerjie, 1910). This was similar to Lombroso's view (1869, 1892) that pellagra was caused by ingesting spoiled maize. The hypothesis advanced by Eijkman (1897) of a poison in rice, whether a toxin produced by disease or a substance in polished rice for which an antidote existed in the pericarp, was widely supported by others (Braddon, 1907, 1909; Bréaudat, 1913; Megaw, 1923, 1930; Teru-Uchi, *et al.*, 1929); some of these workers were not off the rails but on the wrong line, since they confused beri-beri with epidemic dropsy, and their observations were correct for this. McCarrison concluded from his studies that a toxic agent produced true beri-beri but that this poison arose not from the dietary rice but was 'generated in the body as a result of the disordered metabolism induced by a certain degree of vitamin-insufficiency'.

This view, as McCarrison stated, was not original. Eijkman believed that the cause of beri-beri might well prove to be a nerve-poison produced by disordered metabolism arising from vitamin deficiency; Funk (1914) and others observed that the effects of deficiency of vitamin B in pigeons were accelerated by increasing the amount of carbohydrate in the diet, and the blood-sugar of polyneuritic pigeons was increased (Cooper and Braddon, 1914; Funk and von Schönborn, 1914; Funk, 1919, who attributed the hyperglycaemia to the hypertrophy of the adrenals found by McCarrison). Walshe (1918), referring to some of this work, concluded: 'What these observations actually prove is that the absence of both "vitamines" and polished rice does not cause polyneuritis, but that, in the absence of the former, polished rice directly causes polyneuritis.' Hopkins (1920) criticized Walshe's reluctance to believe that a negative factor, such as absence of a vitamin, could be the sole direct and immediate cause of a disease such as beri-beri or scurvy: 'There may be a toxic factor even in typical uncomplicated beri-beri, but without direct evidence for it it seems unnecessary to drag it into etiology by the heels.' McCarrison, who had found as others had done before him that a high carbohydrate diet intensified deficiency, concluded from his further experiments: 'I am led, therefore, to conclude that the ultimate cause of true beri-beri is a poison produced in the course of a disordered metabolism arising out of an insufficiency of the anti-neuritic fraction of vitamin B, and that the view propounded by Eijkman many years ago, and so ably defended by Walsh[e], is in essence the correct view, though starch is not necessarily the source of this poison.'

Various attempts were made to identify the toxin. Certain Japanese workers thought they had found it in methyl glyoxal, and Findlay (1921) showed a decreased concentration of glyoxalase in liver in avian polyneuritis. A most interesting paper from Japan (Kato, Shizume and Maki, 1921), which has been largely overlooked, showed that in avian polyneuritis, but not in inanition, the conductivity of nerves was impaired; the disturbance could be reproduced by the action of hydrogen ions on the nerve; paralysed nerves and the blood of paralysed pigeons or fowls were found to have an excess of hydrogen ions whereas starved birds were normal in both respects. The rapidity of the cure of avian polyneuritis precluded a histologically demonstrable lesion in the nerves, 'but if we consider the paralytic state is due to the action of some toxic substance such as hydrogen ions on the nerve and the recovery is effected by removing them with injection of the rice bran extract, the entire phenomenon is easily conceivable'. McCarrison, in a study with Sankaran of the pH of organs in pathological conditions eleven years later, showed a significant decrease in the brain and ventricle of the heart. Meanwhile Collazo and Morelli (1925) had found increased lactic acid in the blood of avitaminotic birds, and Japanese workers (Inawashiro and Hayasaka, 1928; Hayasaka, 1929) in the blood of patients with beri-beri. Peters showed that in deficiency of the anti-neuritic vitamin lactate accumulated in the lower parts of the brain and other tissues (Kinnersley and Peters, 1929; Fisher, 1931); it was supposed that when a certain concentration was reached in the lower parts of the brain, opisthotonos resulted (Kinnersley and Peters, 1930). Iwata (1928) believed that furfural, arising from incomplete degradation of carbohydrate, affected the medulla and other parts of the nervous system in polyneuritis in pigeons and in rats deficient in vitamin B. In discussing this, Peters (1930) concluded: 'Our work points to a medullary origin of the symptoms perhaps, but makes the toxic product an excess of the normal metabolite, lactic acid.' Later Peters showed (1933 and onwards, cf. 1936) that thiamine was concerned in the oxidation of pyruvate in the brain, and that in deficiency there was an increased concentration of pyruvate in the blood and tissues; since pyruvate inhibits the oxidation of lactate, this also accumulates. He stated (1939), however, that it was an error to think that pyruvic acid was a toxic agent. More recently, evidence has accumulated which makes it probable that pyruvate, accumulating in deficiency of thiamine or from some cause that inhibits pyruvate degradation as in arsenic poisoning, is in fact toxic (Nitzescu and Angelescu, 1942; Dobrovolskaïa-Zavadaskaïa, 1946; Draper and Johnson, 1951), and its accumulation may be responsible for the anorexia of thiamine deficiency.

McCarrison did not believe a toxic substance was the cause of the signs in all forms of thiamine deficiency. He followed Eijkman's (1897) classical work on *polyneuritis gallinarum* with a detailed study in 1,680 pigeons of *polyneuritis columbarum*, which he carefully distinguished from *beri-beri columbarum*; in the former, in which there was cardiac atrophy, inadequacy of the anti-neuritic fraction of vitamin B was the cause, but in 'true beri-beri' in the pigeon there was cardiac hypertrophy and the deficiency of the vitamin produced a toxin. *Beri-beri columbarum* could be wet or dry, depending upon whether or not there was hypertrophy of the adrenals; deficiency of protein was not a factor in the causation of the oedema. He emphasized that these conditions were analogous to beri-beri in man, and made a very extensive inquiry into the occurrence of the disease on different diets. Peters (1930) disputed McCarrison's view that true beri-beri arose from deficiency of vitamin B; he suggested that McCarrison did not find a strict correlation between beri-beri and oedema because the presence of oedema may sometimes be masked by the absence of salt—an important factor—and Peters provisionally thought that thiamine together with an anti-oedema factor, which was possibly vitamin B_3, was equivalent to the anti beri-beri vitamin: 'Our work has brought us very near to Vedder's old hypothesis of the necessity of two vitamins for protecting against beri beri. Since the giving of large amounts of B_1 does not prevent the appearance of beri beri, McCarrison's view that the condition arises owing to a diminished amount of B does not hold *sensu stricto*.' Mellanby (1934) supported the idea of two vitamins but introduced new concepts: 'In a word, it would appear that the actual polyneuritic changes of beri-beri are not due to a deficiency of vitamin B, but to vitamin A. . . . All the evidence shows, however, that vitamin B_1 is not related to the polyneuritic changes associated with demyelination, but that a vitamin A deficiency is responsible.'

There is now probably general agreement that all four forms of beri-beri—wet, dry, acute cardiac and convulsive—with the mixed types are caused by deficiency of thiamine. The type produced is probably conditioned by several factors: degree and duration of dietary deficiency of thiamine, amount of carbohydrate in the diet and ratio of energy obtained from non-fat and fat sources; amount of salt ingested; age and activity. McCarrison stated that: 'Wet beri-beri and dry beri-beri are essentially the same disease; the former differs from the latter in the greater derangement of the adrenal glands.' This is probably true, although his attribution of the oedema to raised intracapillary pressure from increased production of adrenaline is not now believed. His studies of the occurrence of beri-beri on different diets, his investigations of rice (extended later by another valuable report from Coonoor by Aykroyd, Krishnan, Passmore and Sundararajan, 1940) and his analyses of the thiamine content of rice (following the work of McCollum, Cooper, Chick and Hume, and others), his refutation of the phosphorus pentoxide standard for the anti-neuritic potency of rice (which was supported as late as 1928 by Vedder and Feliciano), and his studies of the pathology of different types of deficiency in the pigeon all added materially to our knowledge.

Though much still remains to be learnt, one may perhaps attempt to summarize the present position tentatively as follows. Thiamine has been proved largely by the important work of Peters to be part of the enzyme system in animal tissues that decarboxylates pyruvate and so brings it into the tricarboxylic acid cycle. Therefore in deficiency of thiamine pyruvate oxidation is decreased and this substance, known to be toxic, accumulates. Diets relatively high in carbohydrate but deficient in thiamine will increase the accumulation, and the diminished metabolism is likely to be particularly important in those cells that have a predominantly carbohydrate metabolism (such as nerve cells) or that use pyruvate extensively (such as cardiac muscle cells). In acute severe deficiency in man, it is probable either that pyruvate accumulates in the lower parts of the brain and causes vascular dilatation and minute haemorrhages with the clinical syndrome of Wernicke's encephalopathy, or that acute cardiac beri-beri is produced; both conditions may respond dramatically to therapy with thiamine. A condition analogous to the former has been studied in pigeons in acute deficiency by Prados and Swank (1942); acute deficiency in swine causes myocardial necrosis and dilatation with sudden death from heart failure brought on more rapidly by exercise (Follis, Miller, Wintrobe and Stein, 1943). Chronic mild deficiency with a diet relatively high in carbohydrate produces dry beri-beri, the failure of nerve function starting distally in the longest peripheral neurones probably because of the toxic effect of pyruvate but possibly because of the lesion in pyruvate metabolism in their cells: it is still logical to believe, despite the evidence of accumulation of pyruvate and its toxicity, that the damage to the cell is not a poisoning, and that a high carbohydrate diet depletes the body of thiamine faster than occurs in inanition or on high fat diets. In chronic deficiency there is anorexia, which is probably a central effect of the pyruvate accumulation; this causes inanition which is accompanied by oedema such as occurs on low calorie diets; in either case there is adrenal hypertrophy and it is possible that the oedema—which will depend partly on the amount of salt ingested—is caused by increased retention of salt in the body. But the clinical picture of wet beri-beri differs from that of famine oedema in one important respect: in the latter condition the limbs tend to be cold and pale though there is often acrocyanosis; in wet beri-beri the limbs are warm and red with a decreased circulation time, probably because of the vasodilator effect of pyruvate.

'STONE'

Osborne and Mendel (1917), and Mendel (1920), found calculi in the urinary tract of 81 out of 857 experimental rats; they believed that 'In every instance where calculi developed, the animals were without an adequate source of the fat-soluble vitamine for some time.' McCollum (1924), however, concluded: 'Osborne and Mendel (1917) observed calculi of calcium phosphate in the urinary tract in ninety-one [*sic*] animals among 857 necropsies. Forty-three per cent of these had not had a satisfactory supply of vitamin A. In McCollum and Simmonds' experience calculi have occurred so frequently in animals whose diets contained an abundance of this factor, but were faulty in other respects, that it would seem to be the result of general debility rather than lowered vitality brought about by specific cause.' Fujimaki (1926) produced calculi in the bladder, kidney and gall-bladder of rats by a diet deficient in vitamin A supplemented at intervals by cod-liver oil.

McCarrison started his work on calculi in the same year (1926), and was concerned as was his custom to use diets that appeared to produce urolithiasis in certain parts of India; he had first made a careful analysis of the distribution of known cases. After producing stone in 250 rats he concluded that excess of calcium relative to phosphorus and also deficiency of vitamin A were important dietary factors in the aetiology in his rats and might well be connected with the cause of urolithiasis in India but not in England. Van Leersum (1928) confirmed his work and suggested that keratinization of the renal epithelium favoured the deposition of calcium. De Langen (1929) and Higgins (1933, 1935) also obtained similar results; the latter, who studied humans and rats, concluded that keratinization of the renal epithelium was followed by urinary infection and alkaline urine, so that calcium phosphate was then deposited; his work was criticized in part by Oppenheimer and Pollack (1937), but O'Conor (1935) supported the importance of deficiency of vitamin A and occurrence of alkaline urine in the formation of calcium calculi. Hou (1935), and Lelesz and Przeździecka (1935) thought excess of vitamin D was an important adjuvant to deficiency of vitamin A in lithiasis, but Perlmann and Weber (1928) appear to have produced deficiency in rats on diets deficient in vitamins A and D; McCarrison excluded excess of vitamin D as a factor in his work. Erickson and Feldman (1937) and Long and Pyrah (1939) thought they had evidence of deficiency of vitamin A from the poor dark-adaptation observed in certain patients with lithiasis, but Jewett and colleagues (1943) obtained no such evidence in their American cases. Lowsley and Kirwin (1944) concluded: 'That lithiasis is a deficiency disease is borne out. . . . Fresh vegetables, milk and cod-liver oil have probably contributed more than any other factor to the lessening of the incidence of urinary stone in childhood.'

There can be little doubt that the increased incidence of urinary lithiasis associated with chronic deficiency of vitamin A arises for the reason McCarrison suggested: keratinization and desquamation of the renal or bladder epithelium forms a nidus and infection rapidly supervenes. Such deficiency is a cause of calcium calculi but, as McCarrison stressed, it is not the only cause.

FAULTY DIETS

At the turn of the century there was much interest in the amount of protein that should be ingested daily. Usually the amount eaten customarily by apparently well-fed groups of persons was assumed to be adequate. Thus Playfair (1865) believed the average English soldier ate about 120 gm. daily, and Voit (1881) gave 118 gm. for a German soldier. For comparable men Rubner gave 127 gm. and Atwater 125 gm. The question arose whether the groups of people would be in better health on larger or smaller amounts. There had been plenty of cranks advocating moderation in protein intake by the use of a vegetable diet: Sylvester Graham in 1829 is a well-known example. And scientific evidence was adduced in support of low protein diets by Chittenden and others, as already mentioned. In Italy the idea arose that subnormal physical development was being produced by low protein diets: the social anthropologist Niceforo (1905) showed that poor children had retarded growth and subnormal weight possibly through such deficiency; Lichtenfelt (1905) thought shortage of protein and calories made the people of southern Italy inferior physically to their northern neighbours; Albertoni and Rossi (1908) achieved good results by giving poor peasants in southern Italy 100 to 200 gm. of meat daily.

At the same time, in India, McCay made the observations to which reference has already been made, and McCarrison was impressed with the magnificent physique and virility of the well-fed Sikhs of the north in contrast with the vegetarian Madrassi of the south with their stunted nature, frequent illnesses and high mortality. He appreciated that genetic differences or environmental factors other than nutrition might play a part; experiment was needed. He therefore did his celebrated experiment of feeding rats upon the diets of the two races. Professor Stare (1944) commented that 'It is of interest that this classic experiment was repeated on rats only a year ago by another investigator, and essentially the same results were obtained'; it was repeated year by year at Coonoor for class purposes. Later, Orr and Gilks (1931) studied the differences in physique and health of two African tribes, the Masai and Akikuyu, and observed a similar phenomenon.

There is now abundant information that improvement of diet effects better health. The evidence derives from observations upon groups of persons on different diets, from the experimental supplementation of human diets, and from experiments upon lower animals. Making use of this information, McCarrison was able to breed animals that caused widespread comment. Sir Alexander Russell wrote: 'For years his rat populations were completely free from sickness and he had no mortality from infections or disease—a marvellous result. I have never seen anywhere animal houses as clean and as free from odour, and never have I seen such sleek, glossy-looking, furred animals as those living in McCarrison's animal houses. The diets the animals were fed on were, of course, the main cause of this wonderful result.'

LECTURES AND ADDRESSES

This volume is concluded with extracts from McCarrison's own lectures and addresses, and a bibliography of his work so that the original articles can be more easily consulted. The request for such public utterances came early: in the autumn of 1921 McCarrison visited the U.S.A. to give a number of lectures by invitation. I vividly remember a lecture given for Sir Rudolph Peters in the Department of Biochemistry at Oxford when I was an undergraduate; it was impressively delivered from scanty notes, these being used to provide detailed evidence mainly from his own experimental work for the broad conclusions he reached. McCarrison sustains his thesis 'that the greatest single factor in the acquisition and maintenance of good health is perfectly constituted food'. He was not concerned in his own work to discover new nutrients or elucidate their mode of action; impressed by the multiple nature of nutritional deficiencies as they occur in man, he chose a different course. With eyes wide open, he intentionally followed the path of Clinical Science instead of that of Experimental Physiology.

Indeed, in India and as a government official, it would have been impossible to work solely on pure nutritional science. In India, 3 per cent of the world's surface carries 20 per cent of its population, and many of her 450 million inhabitants are in a state of chronic malnutriture. The infant mortality is very high: only half the children born live to be 20 years old, two-fifths die before they are 5, and a quarter of the infants die in their first year. The expectancy of life is only 26 years. The incidence of ill-health, and especially the toll of infectious disease and the poor physical development, are one side of the problem; the periodic disastrous famines are another. McCarrison by his own work showed how these problems can and should be studied, and he created the great Nutrition Research Laboratories where Indians are now actively carrying on the work he started. He wrote: 'The problem in connection with all these diseases is no longer one of lack of knowledge of their nature, nor of their means of prevention; but one of the improvement of conditions of living and of food-supply of the people. Indeed, the greatest of all problems in India at the present time is the adjustment of the population to its food-supply. It is one that is capable of solution only by the people themselves: by the exercise of self-help; by the jettisoning of old habits and customs unsuited to modern economic conditions; by improvement in methods of agriculture, animal husbandry and industry; and, above all, by restraint in reproduction.'

In this note, which Dame Harriette Chick and Dr. Passmore have kindly read in typescript, I do not intend to assess McCarrison's place in the history of nutritional research. I conclude with remarks made nearly a quarter of a century ago by Garrison in his *History of Medicine* (1929). 'One of the last and best of the noble line of the Indian Medical Service is Lieut.-Col. Robert McCarrison (1878–　　), who entered the service in 1901, and has been on almost continual duty in India to date, latterly at the Pasteur Institute at Coonoor. In 1906, he described the three-day fever endemic in Upper India since 1895, which is probably identical with Dalmatian pappataci fever. He is further distinguished by his investigations of the infectious endemic goitre of Kashmir (1913), the thyroid gland (1917), beriberi and other deficiency diseases (1921–4), particularly the remarkable degenerative changes in the viscera and general lowering of digestive capacity produced by vitamin B- or C-deficiency anterior to beriberi or scurvy. This is one of the most significant contributions to the role of nutrition in preventive medicine.'

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II. THE PROBLEM OF GOITRE

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There has been a great quickening of interest in goitre during the last decade, due in large measure to the introduction of the thiourea compounds exactly ten years ago. At the present day, when it is probably true to say that more is being written about the thyroid gland than is ever read, it is most refreshing to pause a while and turn back to Sir Robert's contributions to this subject. Any worker in this field who has not already done so will find such reading a most rewarding task, for there are few aspects of the goitre problem upon which Sir Robert did not touch. The remarkable thing is that so much of his work has lain unrecognized; possibly this is because it was not always published in readily accessible places. The thirty years which these investigations spanned, from 1905 to 1935, can be divided into a number of periods governed largely by the availability of clinical material or the facilities for research on animals or humans.

At the beginning of this century, McCarrison first became interested in goitre in the nine villages which make up Gilgit in the foothills of the Himalayas. In eight of these, goitre was endemic, and when the degree of endemicity was high, congenital goitre, cretinism, deaf-mutism and idiocy were common. In one village, however, goitre was virtually unknown, and this appeared to be related to the fact that it had a separate source of drinking water from a particularly pure mountain spring. The other eight villages were located one below the other on the same water supply, and as the water descended it became more and more polluted with human and animal excreta. A goitre survey showed that the incidence became greater as the water became more polluted, and from this most important observation stemmed practically all the subsequent investigations and experiments. The importance of this observation was that it drew attention to the likelihood of some noxious substance being present in the water as the main factor in causing these goitres. This is in sharp contrast to the other approach to goitre aetiology which relates the thyroid hypertrophy to lack of iodine in the diet. Not that this second factor was overlooked by McCarrison; indeed, he carried out an immense number of investigations on iodine intake which clearly showed that iodine lack was an important factor in goitre production both in humans and animals. However, he realized early that a number of different factors were at work in producing endemic goitre and thus set about investigating each in a methodical manner.

Endemic goitre so commonly occurs in mountainous areas that many have tried to relate it to various geological factors. However, by 1927 we find Sir Robert reporting to the International Conference on Goitre in Berne that: 'I have not been able to satisfy myself that any close correlation exists between the endemicity of this disease and certain geological formations . . . but that the endemic was met with more frequently on the older than on the more recent formations. This is my opinion to-day.' His work upon pigeons showed that the addition of much lime to the diet caused a significant increase in the size of the thyroid gland, an increase which could be prevented by the addition of more iodine to the food. Nothing significant has been added to these findings since that time.

Probably no research of Sir Robert's on goitre gave him so much satisfaction as the experimental induction of thyroid enlargement in man, more especially as he was successful in producing a goitre in himself. This was in 1906 and it was carried out by giving his volunteers and himself a twice-daily drink of 6 oz. of the suspended matter removed from the grossly polluted, goitre-producing water in Gilgit. Only about one-third of the volunteers developed thyroid swellings, no goitres appearing in those who drank the water after it had been boiled. The enlargement usually made its appearance between the tenth and fifteenth day of the experiment, reaching its maximum size between the twenty-fifth and thirtieth day. One feels that here was a most potent goitrogen whose characteristics were not unlike those of the thiourea derivatives. Whether the actual bacteria present, or some toxin or other substance produced by them was the cause, Sir Robert is at pains to leave unspecified. As in all his work, he is scrupulously careful in his deductions and in his attempts to control all the variables of his experiments. He did in fact determine the iodine content of the water and found it to be of an order sufficient under normal conditions of diet. There are a number of records in the literature concerning epidemics of thyroid enlargement, but this appears to be the only occasion on which one was experimentally induced.

It is a remarkable coincidence that another well known investigator of thyroid problems, David Marine, also studied an epidemic of goitre due to water pollution early in the century (1909–10), but in his case the subjects were trout. He found that hyperplastic goitre occurred in artificially-reared trout confined in tanks located one above the other on the same water supply; the effluent from one tank flowing into the next below it in the series. The incidence of the disease increased from the first to the last tank. This was a remarkable confirmation of the observations made earlier on man in Gilgit. Marine also concluded that some goitrogen was at work, but in later years he thought that the absence of iodine was of more importance than the presence of any noxious substance. At the present day, when attention is once more being focused on the existence of a great many goitrogenic substances in the everyday diet of most people, Sir Robert's views ring remarkably true. Had some goitrogen such as thiouracil been present, precisely similar observations might have been made in his surveys. The hyperplasia in the trout might similarly have been induced. Such observations do not in any way detract, however, from the valuable work done by Marine, Kimball, and others, in introducing iodization of table salt. The effects of almost all goitrogens can be successfully counteracted by giving added iodine in the diet.

In 1928 Chesney in Baltimore made a most fortunate discovery whilst investigating experimental syphilis in rabbits. He found that a diet composed almost exclusively of cabbage led to goitre production and the longer the cabbage was given the bigger was the goitre. McCarrison immediately realized the significance of this discovery; here at last was a goitrogen which occurred naturally and could be used for investigation. He found that winter cabbage was more potent in increasing the size of rabbits' goitre than the summer-grown vegetable and young animals were more easily affected than old ones. Further work showed that the iodine content and calcium content of the outer leaves might be from twenty to thirty times as great as the inner. The type of goitre produced was very like that resulting from the ingestion of contaminated water in Gilgit but no organisms were found in the cabbage. Finally, a great many further experiments were carried out to find what the goitrogen was and what substances might counteract it. Sir Robert's conclusions are worth quoting because they show that he had already grasped the full implications of this discovery which, a few years after his retirement, led Purves and his associates in New Zealand to the work on rape-seed and shortly thereafter Astwood, to the discovery of thiouracil. The conclusions were these: 'Nevertheless, several important facts have emerged from these studies: the existence in certain food-materials of *positive* goitrogenic factors—as opposed to the *negative* one of iodine-deficiency has been demonstrated, while it has been shown that substances which depress cell oxidation may increase thyroid activity and that cyanides are to be included in this category.'

Sir Robert McCarrison's goitre surveys and his conclusions on how they should be carried out and how the results should be assessed remain to-day our best guide to this kind of work. His attempts to relate thyroid size to body size were valuable, especially since they led him to the fact that at puberty the thyroid gland attains a greater size in relation to the body than at any other age, thus puberty-goitre is not a true criterion of the endemicity of the disease. It is true that a goitre survey can more easily be carried out by visiting schools and examining the children, and undoubtedly a guide to the amount of goitre in the area can be determined in this way. It was while conducting goitre surveys that McCarrison became interested in the value of the statistical method in which he was a pioneer.

With the passage of time Sir Robert became more and more the laboratory research worker. To this field he brought his wonted enthusiasm and thoroughness and the animal houses at Coonoor were a model for the others to follow. The standards of cleanliness he adopted followed naturally from his observations on the production of goitre from the ingestion of excreta. In these laboratories he carried out his work on cabbage goitre. He also studied the goitrogenic effects of an excess of fat in the diet, and investigated the goitre-producing qualities of soya bean and cyanide and noticed the changes resulting from a scorbutic diet. This work has all stood the test of time and only in recent years has its importance been properly appreciated. Perhaps one particular group of experiments should point the way to further investigations along the same lines to-day. This was the production of lymphadenoid goitre by means of a diet whose main feature was a severe lack of vitamin A, though it contained adequate amounts of iodine. Others have not been able to repeat this work, almost certainly because they could not obtain the same quality of material in their diets. Or, again, it may have been due to the different strains of rats used, for it is well known that certain strains of rats are peculiarly susceptible to certain varieties of disease. It would be of particular value to be able to produce Hashimoto's disease or lymphadenoid goitre experimentally as this is a disease which is by no means uncommon among the population in England and America. Moreover, it is being recognized much more frequently by pathologists at the present day. It almost always produces myxoedema as an end-result and it is a condition not often recognized before the surgeon has performed a thyroidectomy, believing the condition to be one of simple goitre. Sir Robert described how its occurrence in his rat colonies was haphazard and sometimes repeat experiments revealed no examples of it. 'Deficiency of vitamin A', wrote McCarrison, 'appears to be the chief cause of its occurrence; but it is not the ultimate cause. It is related to some peculiarity, constitutional, toxic or microbic, of the individuals affected by it. The diets associated with its occurrences have definite effects on the thyroid gland. Of these the formation of keratinization cysts is the most constant; colloid accumulation—amounting sometimes to the production of small colloid goitres—comes next in order of constancy; the aggregation of lymphocytes, is the least constant feature.'

In this brief attempt to appraise the work of Sir Robert McCarrison in the field of goitre it is important not to overlook his insistence on the use of proper statistical methods in the interpretation of results obtained from animal experiments or human surveys. In association with Professor K. B. Madhava he published a memoir, *The Life-Line of the Thyroid Gland*, in which the results of thyroid measurement were related to the body-weight of the individual. In addition, the normal mean size of the gland was established for individuals included in certain categories of body-weight and categories covering various age groups. It was as a result of this work that the incidence of goitre in school children was shown not to be a true criterion of the endemicity of the disease. Many so-called childhood goitres were not pathological, but were the normal physiological expression of the organ's place in relation to the growth and development of the child. This insistence on the use of the statistical method in interpreting the results of human and animal measurements was a pioneering move. Its importance was not to be appreciated for many years afterwards.

In December 1952 the World Health Organization called together a small study group to discuss endemic goitre. Delegates gathered in London from such widely separated countries as Mexico, Australia, India, Yugoslavia, the United States and Switzerland. It was not long before the name of Sir Robert McCarrison was mentioned and it cropped up repeatedly thereafter. Surely no greater compliment could be paid to him than this, that his pioneering studies in the field of endemic goitre should still form the basis of much that we believe to be true to-day. Indeed, it is remarkable how little new has been added to our knowledge of this world-wide disease since Sir Robert's communication to the Second International Conference on Goitre in Berne in 1933.

It has been both a privilege and an honour to have been asked to contribute to this volume. It is a task that I have found difficult, for Sir Robert has made so many additions to our knowledge of simple goitre that it has not been easy deciding what to omit. I know of no one else alive to-day who has contributed so much that is new to so many varied aspects of the goitre problem. His contributions still remain valid in the light of newer knowledge of thyroid physiology gained largely from the use of radioactive iodine and the thiourea derivatives.

The Work of Sir Robert McCarrison

CHAPTER I

Researches on Fever, 1902–1904[1]

Sailing[2] for India on my twenty-third birthday, fresh from the medical schools and but a child in knowledge, it chanced that the earlier years of my service were spent in the remote regions of Chitral and Gilgit where nature makes large-scale experiments upon man. It is of some of these experiments, and of my attempts to observe and to control nature's ways in making them, that I have to tell. There is, too, this reason for the telling of them: that after devoting many years of my life to the investigation both of naturally occurring disease in human beings and of experimentally induced disease in animals, I am convinced it is only by study of the experiments which nature makes upon man—the complex, the mutable, the variable—that we shall reach final solutions of the causes and origins of the diseases to which he is subject. This is not to decry the experimental method in research, to which modern medicine owes so much, but to insist that it must be the coadjutor and not the master of those who seek in man himself and in the circumstances of his life for the causes and origins of human ailments.

Chitral and Gilgit

Following a line due north from Bombay, through Gujarat and the plains of Rajputana, across the five rivers of the Punjab, on by way of Malakand, Swat, Dir and the Lowari Pass, we come at length to the little principality of Chitral at the extreme north-western boundary of the Indian Empire. About the size of Wales, it lies wedged between Kafiristan and Badakshan on the one side and Yasin, Punyal and Gilgit on the other. To the north it is bounded by the outstretched eastern arm of Afghanistan, to the south by the high mountain range that forms part of the northern watershed of the Indus. Made up of the precipitous spurs and slopes of the Hindu-Khush this mountain-girt and mountain-intersected region is—but for oases of cultivation on alluvial deposits at the mouths of its narrow valleys—barren, desolate and wild. Here the inhabitants, formerly as turbulent as the torrents that traverse their territory, were reduced to order by the campaign of 1895; and, in the days of which I speak, 1902–4, a relatively small garrison of Indian troops served as warden of these frontier marches.

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[1] Papers relating to these researches will be found in the Bibliography, p. 308.

[2] Extract from Lloyd Roberts Lecture, number 145 in Bibliography.

Northward through Chitral and Mastuj, then eastward by way of the Shandar Pass, we reach the Gilgit Agency, comprised of seven little principalities with Gilgit itself—the capital of the district. To the north are the Pamirs, with the source of the Oxus; to the west, Chitral; to the east, Baltistan and western Tibet; to the south, the great Himalayan range and the passes to Kashmir. Through it great rivers run to join the Indus as it cuts across the district in its tortuous way to Punjab, Sind and sea. Here, robed in perpetual snow, are Dubanni, Rakapushi, Haramosh and Nanga Parbat, raising their majestic heads to heights of 21,000 to 26,500 feet above sea-level. Here is the place of the high hills, here the place of glaciers and glacier-born torrents, here is Bam-i-Dunya—'the roof of the world'.

In these regions I spent the years from 1902 to 1911, first as a regimental medical officer in Chitral (1902–4) and later as Agency Surgeon in Gilgit (1904–11); combining with my official duties the study of certain diseases that were prevalent there. This was no bad combination; for as a military medical officer my duty was to maintain the troops in health and to search out the causes of their ailments, while as Agency Surgeon I had ample opportunity for professional work both surgical and medical; an experience that proved invaluable when in later years my activities were confined to the laboratory. Thus, when called upon to study 'stone' in human beings my familiarity with it on the operating table and with the manner of life and food supply of those who suffered from it, helped greatly in the devising of experiments for its production in animals and in the discovery of positive and negative factors concerned in its causation.

THE THREE-DAY FEVER OF CHITRAL

October 1902 found me quartered with my regiment in the Fort of Drosh, Chitral. The winter months, dreary, desolate and cold, left our health unharmed, but with the advent of the hot, dry months of summer, there fell upon us a strange sickness which few escaped. It came upon us stealthily—*phīk-bī-thi*, as the Chitralis themselves expressed it. Up to the end of the second week in May there were no cases of it or none that were recognized as such; by the end of July more than one-half of the garrison had suffered from it. The malady was a single paroxysm fever with intense frontal headache and pains in the back, bones, joints and muscles, lasting, as a rule, three days and followed by severe prostration. What was this disease that one day, as it seemed, left the troops unharmed and the next smote them by the score? Since the date of our occupation of Chitral it had been returned officially as 'ague' and much quinine had been expended in attempts to prevent and cure it. Few of my predecessors appeared to have seriously regarded it as malaria, but as field service conditions in those days provided no laboratory equipment, their difficulty, like my own, was to find a suitable diagnostic label for it. Clinically it differed from malaria and when the controlled use of quinine as a therapeutic agent had shown that sufferers from it recovered as quickly without the drug as with it and that the prophylactic use of quinine was useless, there seemed to be little doubt of the non-malarial nature of the malady. It was not influenza; nor could it be dengue, though in some respects it resembled this breakbone fever, for there was no rash nor terminal fever, both characteristic of that condition. Manson's *Tropical Diseases* of that day—my sole book of reference—included no malady with which it could be identified. Apparently, therefore, I had to deal with a new disease.

It was customary for the garrison to be relieved each year in the month of October, and each summer the same story was repeated; large numbers of the men of each new garrison suffered from this fever. Fortunately for my study of it there was one year, 1898, in which the garrison was not relieved and my predecessor of that time had recorded that during the summer of 1899 'there was very little fever amongst the troops'. An examination of the hospital returns revealed, however, that they had suffered severely during the previous summer. Here was an observation of moment: why had they suffered during their first summer in Chitral but not during their second? An acquired immunity suggested itself as the answer; an answer which my subsequent investigations proved to be correct.

Having decided that I had to do with a new disease, the first necessity was accurately to record its clinical features. This was rendered easy by the two attacks from which I myself suffered and by careful case-taking in some hundreds of others. The next step was to study its epidemiological features, a study facilitated by the experiments which military dispositions and my own curiosity made upon the troops. It was found, for instance, that when bodies of men were moved, during the height of the epidemic, from the Fort at Drosh to a camp a few thousand feet above it, cases of the disease occurred amongst them during the first few days of their residence in the camp but none thereafter; it did not spread amongst them. On their return to the Fort cases began to appear within five days of their arrival amongst those who had not previously suffered, very rarely amongst those who had. It was found, moreover, that a single night spent in the Fort, or even a stay therein of only a few hours, was sometimes followed by the appearance of the malady amongst such sojourners. Clearly, then, this was a place disease; it did not occur above a certain altitude; it was not contagious; and, its incubation period was five days or less. Investigation of its relation to atmospheric temperature revealed that it did not appear, or not in epidemic form, until the mean atmospheric temperature reached 75° F. and that it disappeared with the onset of the colder weather of early autumn. Rainfall, scanty during the summer months, had little or no effect on the course of the epidemic. But the appearance, disappearance and distribution of the malady appeared to correspond, in a remarkable way, with the appearance, disappearance and distribution of the sand-fly. Beyond this my investigations could not go in 1903. Another year in Chitral was needed to complete them, and a considerable resolution on my own part to induce me to stay there for their completion. So October 1903 saw my own regiment march out and one strange to me march in. The winter months provided time for reflection, for the analysis of records, and for the devising of plans of campaign for the following summer. Inquiry into native knowledge of the malady—a procedure not to be despised—revealed that it did not occur in villages located at heights of 6,500 feet or over; that in those where it did occur young people and strangers suffered most; and, that it was more likely to occur in those who slept indoors or near mud buildings. My records showed that young soldiers suffered most, that second attacks were rare, third attacks rarer still and fourth attacks unknown. It was evident, therefore, that immunity was acquired by previous attacks. The chief problem then was to discover how the disease was spread. There were two possibilities, as it seemed to me: infection by way of the nose and throat and suctorial insects. The high incidence of catarrh of the throat suggested the former, the plague of sand-flies during the summer months suggested the latter. To-day the thought of an insect vector seems an obvious one, but in 1903 the idea was still novel, certainly in connection with short fevers. Preparations were accordingly made to meet these possibilities. My student's microscope was sent to me from India, as well as some slides, coverslips and stains. Materials for the making of a few simple culture media arrived; an incubator and sterilizer were improvized from kerosene-oil tins. Thus equipped I faced the future. Prior to the time of the expected epidemic the Fort was disinfected and re-whitewashed, sand-fly-proof nets were provided and attempts were made to teach the me o use them as protective coverings and not as sand-fly traps. A watch vas kept for the first appearance of the disease and a sequence of more or less isolated cases was found to herald the coming of the epidemic. This, when it came at its accustomed time, was less severe, so far as numbers attacked were concerned, than in the previous summer; possibly, as I thought, because of the measures of disinfection or of the use of sand-fly nets. Hundreds of blood smears were examined for malarial or other parasites, but none were found. The infective agent, if it existed in the blood, was invisible to me. (It did, in fact, prove to be an 'invisible virus'.) Material obtained by puncture of the spleen revealed no organism; such blood-cultures as my limited equipment enabled me to make were negative. Nor could the disease be conveyed from the sick to the healthy by smearing the pharyngeal secretions of the former on the throats of the latter. Mosquito surveys did not suggest a mosquito as the transmitting agent; suspicion of the sand-fly became more insistent. Despite my failure to find an infective agent in the blood, attempts were made to transmit the malady from the sick to the healthy by subcutaneous and intravenous inoculations of blood taken from sufferers at the height of the fever. These attempts failed, except, possibly, in one case in which the temperature rose slightly on the fifth day after the inoculation. But this failure was not without its lesson. The volunteers who had submitted to these inoculations were all natives of the plains of northern India. It appeared possible that they might have been immune. A re-examination of my records from this point of view revealed that the incidence of Chitral Fever amongst members of the garrison who were natives of the plains of India was much less, and in those who suffered from it mild attacks were much more common than in Goorkhas and their British officers whose home stations were at altitudes of 6,000 feet or over. On these grounds I predicted that this 'three-day fever' would be found to prevail in other parts of India—a prediction that proved to be correct. By this time my suspicion of the sand-fly urged me to attempt the transmission of the malady by its means. Accordingly, a special box was devised, having a muslin sleeve at one end, into which numbers of sand-flies, that had fed on sufferers, were placed. This box was then taken to the camp above the Fort where men, who had not previously suffered from the malady, by turns inserted the hand and forearm into it while I hoped that the sand-flies, when again hungry, would by their bites transmit the disease to them. But my hopes were vain. For either the sand-flies died at this unaccustomed altitude—their usual fate—or if they bit, their bites were ineffective. Again and again I made these attempts, always to meet with failure, and I left Chitral, on transfer to Gilgit, without proof that the blood was infective or that the sand-fly was the transmitter of the 'Three-day Fever of Chitral'. Under this title I described the disease in the Medical Press.

Meanwhile my conviction that the blood was infective and the sand-fly the transmitter of the infecting agent had become so strong that I resolved, if opportunity offered, to revisit Chitral, there to repeat my experiments. This opportunity came in the spring of 1908, and the long journey to Chitral was begun. But I was not destined to complete it; being recalled on urgent duty to Gilgit, after travelling some fifty miles towards my goal. The opportunity did not recur. So, on the verge of the discovery, made later by Doerr, I left the arena defeated but not without experience gained in the encounter. Soon it was recognized that a disease similar to the 'Three-day Fever of Chitral' prevailed in parts of India, Dalmatia, Herzegovina, Malta, Crete and other Mediterranean stations. But as Manson said of it, in the 1914 edition of his *Tropical Diseases*: 'Its definite relation to its transmitting agent, though suspected by McCarrison in 1903, and by Taussig in 1905, was not established till 1908, when Doerr published his observations of the infectivity of the blood in this form of fever and the role of the sand-fly as its transmitter.'

Thus, the 'Three-day Fever of Chitral' disappeared from the text-books, became merged with 'Sand-fly, Pappataci, or Phlebotomous Fever', and my connection with it a memory. But a memory pleasant to recall and one pertinent to my present theme: that, even without, or with but few, laboratory aids to research, it is sometimes possible, by a study of the characters of human ailments and of their behaviour under varying conditions of life of human beings, to get close to their causes. Further experience was to teach me that these methods of investigation were fundamental; for they indicated directions in which research might profitably be undertaken in the laboratory, served to control and to correct the results of such research, and were themselves corrected and controlled by laboratory findings.

CHAPTER II

Researches on Goitre and Cretinism, 1905–1935

Another experiment,[1] on the grand scale, which nature makes upon the people of these regions is one that results in 'goitre': a malady that soon began to excite my keen interest. At that time (1902–4) little or nothing was known of its causation. I, certainly, knew nothing; and my few books of reference, limited to students' manuals, had little to say of it. Probably my ignorance was no bad thing, for I approached the problem *de novo*, without preconceptions.

My studies began with the survey of goitre in a number of villages. These surveys were not confined to children but included every individual in each village whose presence for examination could be secured. They revealed a number of facts, all new to me, but some of which, as I was later to learn, had already been observed in other parts of the world. The prevailing goitre was the parenchymatous or adeno-parenchymatous type: the classical 'endemic goitre' of certain mountainous countries. Some villages were found to be free from it; in others its incidence was slight; in yet others it was high, often very high. In those villages where it did prevail the inmates of certain houses might be free from it, while their neighbours suffered, though this was rarely so when the endemicity of the disease was high. The sex-incidence varied with the degree of endemicity: when high the two sexes were affected in almost equal proportions, when low the malady was confined mainly to females. Persons of poor estate were more often goitrous than those of a higher social order, and their goitres were usually larger and more degenerated. Congenital goitre, cretinism, deaf-mutism and idiocy were more common in villages where the adult population was severely affected and poverty rife. Hyperthyroidism was conspicuous by its rarity; hypothyroidism of minor degree was common, particularly in goitrous women. In some localities the disease appeared to be associated in its origin with limestone rocks, in others it did not. Many years were to pass before I realized that there were a number of goitrogenic agents, amongst them lime, and that the absence of one of them from one locality did not necessarily preclude its influence in another where it did exist.

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[1] Extract from Lloyd Roberts Lecture, number 145 in Bibliography.

In my endeavour to find the cause of the disease I met with much that was strange, and had some unexpected experiences which determined the lines of investigation I was subsequently to follow. The first of these experiences relates to the differing incidence of goitre in the nine villages collectively known as Gilgit. These are situated on an alluvial fan having an area of a few square miles. Eight were located one above the other on the same water supply. This reached them, from a snow-fed mountain stream, in surface channels or *kūls*. In its passage to and through the villages it was subject to gross pollution by human and animal excreta. The ninth village—Barmis—was located some distance apart from the others, close to the mountainside. It had its own water supply: a spring of exceptional purity, which was not subject to pollution. This village was free from goitre. The disease prevailed in the other eight, but not with the same intensity in each. Its incidence increased gradually from above downwards on the water supply. In the first village 11·8 per cent of the general population were goitrous; in the last—Kashrote—45·6 per cent. Further, the increasing incidence was temporarily checked at one point where the spring water from Barmis joined the main channel. (Four years after these observations were made, Marine reported a similar experience in trout reared artificially in tanks situated one above the other on the same water supply. Even the temporary check in increasing incidence of goitre, from the tank highest to that lowest on the water supply, was observed to follow the junction of a side-stream with the main supply.) These observations led me to think that the increasing incidence of goitre might be due to the obviously increasing impurity of the water. If this were so, it might, I thought, be possible to cure early cases of the disease by the administration of intestinal antiseptics. Trial of these drugs proved that they did cure such cases; thymol being the most efficacious of those used. From this it appeared that they acted by counteracting some goitre-producing agent at the intestinal threshold. It was found, also, that 'soured milk' and shock doses of various vaccines cured early cases of goitre; and that whatever the method of cure—iodine, thyroid extract, intestinal antiseptics or vaccines—minor evidences of hypothyroidism disappeared, the face becoming less puffy and the complexion less sallow.

These observations suggested that goitre was related in its origin to some living agent contained in the polluted water. They led me to carry out certain experiments on man or more properly to study, under strictly controlled conditions, the experiment which day-by-day nature was making upon the villagers of Kashrote. The experiments were designed to learn whether or not the water of Kashrote contained in suspension any agent capable of causing goitre in man. Thirty-five young men, newly arrived from India, were, at various times and in different batches, encamped near my house on the outskirts of Barmis—that goitre-free oasis in a land of struma. They were well rationed; their rations for the most part being imported from India. I, myself, joined their numbers, while continuing to live in my own house and to eat my accustomed food. We obtained our drinking water from the Barmis spring which was known to be non-goitre-producing. Each morning we consumed large quantities of the suspended matter separated from the water issuing from Kashrote. Each experiment lasted fifty-five days. The results were as follows: 10 of the 36 volunteers developed noticeable enlargements of the thyroid gland—fortunately I was one of them. Five had transitory swellings of the organ and 21 were unaffected. I say 'fortunately I was one of them', for the occurrence of goitre in one's own person leaves no room for doubt as to the positive nature of the results of these experiments. Coincident with them, 31 other young men consumed, in the same circumstances, the same suspended matter after it had been boiled. None developed goitre. It seemed, from these results, that the suspended matter contained a goitrogenic agent—a *contagium vivum*, as I supposed—which was destroyed by boiling.

Another experience came a few years later (1913–14), when I had left Gilgit. There was at Sanawar, not far from Kasauli, in the outer Himalayas, a large boarding-school, accommodating 500 boys and girls, the children of domiciled European and Anglo-Indian parents. Goitre had prevailed in this school since its foundation in 1848. At the time of my inquiry no less than 66 per cent of the girls, aged 15 years and over, were the subjects of goitre. To make the story of a long, tedious and exhaustive investigation short, it may be said that the water supply of the school—a spring—was found to be subject to bacterial pollution by human and animal excreta. To this the disease was attributed. I recommended the introduction of a new and well-protected supply, piped from the neighbouring town of Kasauli where goitre was not endemic. This was done, and a few years later goitre had disappeared from the school, although the new water supply contained no more iodine, indeed rather less, than the old. Reporting on this matter in 1921, the Assistant Director of Medical Services in India wrote as follows: 'Since the Kasauli water supply has been piped to Sanawar there has been a complete absence of goitre.' It may be added that no other change was made in the conditions of life of the children.

While these investigations were in progress research was proceeding in the laboratory on lines suggested by the observations made in man. As a result of this research it was found that goitre could be produced in adult animals, and congenital goitre and cretinism in their offspring, by the administration of faecal filtrates or of cultures of faecal bacteria together with their toxins.

These researches, interrupted by the Great War, were resumed in 1918, and continued, as opportunity offered, up to 1935. As long ago as 1849 Provost had propounded the view that endemic goitre was related in its origin to iodine deficiency in the soil and foods produced upon it. An investigation of the problem from this point of view was undertaken. It was found that while a low iodine content of the soil was, in Himalayan India, frequently associated with the occurrence of goitre, this association was not invariable. The cultivated soils of one village might be as low in iodine as those of another, yet goitre be present in the one and not, or only to a slight extent, in the other. The inverse relation between the iodine content of the soil and the incidence of goitre, reported from certain other parts of the world, did not hold good for India. No invariable relation existed between the iodine content of drinking water and the incidence of goitre. These reults, reached in regions whose inhabitants were entirely dependent on the produce of their own lands, were of great importance; for there were no sources from which the people could derive iodine other than that afforded by their own produce. To this rule there was, however, one exception—rock salt. This was imported. It was found to contain appreciable amounts of iodine and to exert, as it appeared, some protective action against goitre. This investigation did, however, provide evidence that in Gilgit the iodine contained in the food and drinking water was deficient relative to the goitre-producing substance or substances contained in polluted water. It was concluded, therefore, that the occurrence of goitre was dependent on factors other than, or in addition to, the iodine content of the soils and of the foods grown upon them.

It became necessary, then, to search for other factors, and to establish, if possible, the relation of iodine deficiency to the disease. The first essential for the proper prosecution of the search was to establish numerical standards of size of the normal thyroid gland and to learn the extent to which this size might vary in consequence of growth, development, physiological states, sex, season and diet. With these standards as the basis of observation it would then be possible accurately to estimate the effects of various factors—dietetic, hygienic, and others—in causing abnormal increase in size of the gland, that is to say, goitre. In this work I was fortunate in having the collaboration of a distinguished statistician—Prof. K. B. Madhava. The results of our labours are set out in a memoir entitled *The Life-line of the Thyroid Gland.* (These are supplemented in my Reports to the First and Second International Conferences on Goitre, held at Berne in 1927 and 1933.)

CRETINISM

Cretinism—that most tragic of the sequelae of goitre—was very prevalent in certain parts of Chitral and Gilgit. Two types of the disease were found: the classical type, and another to which I gave the name 'nervous or tetanic cretinism'. The former corresponded to that met with in Europe; the latter was a condition in which the cretinoid state was associated with tetanic spasms, nystagmus, strabismus and spastic paralysis of the limbs. Combinations of both types frequently occurred in the same individual. The former was the more common amongst the less poverty-stricken of the people; the latter the more common amongst the poorest classes. The mothers of cretins were almost invariably the subjects of adenomatous goitre. They usually showed signs of hypothyroidism, and commonly suffered from tetany, arthritis deformans or other ailments. It is interesting to recall that tetany—endemic in certain parts of the Gilgit agency—was confined almost exclusively to females and was curable by the administration of laxatives and thymol.

The therapeutic use of fresh thyro-parathyroid extract, made from the glands of sheep, caused marked improvement in both types of cretinism; the nervous symptoms responding to this treatment in a remarkable way. I had read of the effects of thyro-parathyroidectomy, as observed by Horsley and by Murray in monkeys, and was impressed by the similarity of the symptoms described by them to those seen in tetanic cretins. It became necessary, therefore, to obtain post-mortem material from cases of this malady; a matter of extreme difficulty owing to the prejudices of the people. Fortunately, some doubt arose as to the cause of death of a cretin of this type and I was able to remove the trachea with the attached thyro-parathyroid glands. But having no means to examine the specimen histologically, it was preserved in formalin and brought to England on my next leave. A friendly pathologist was good enough to section it for me. The thyroid gland, though not much enlarged, was found to be extensively fibrosed and to contain areas of compressed glandular tissue. No trace of parathyroids could be found. It appeared, therefore, that both the thyroid and the parathyroid glands were involved in this case and probably, also, in others of the same kind. Some years later (1913–14) I succeeded in producing, under experimental conditions in rats, a similar involvement of the thyro-parathyroid glands.

[The extensive work on goitre and cretinism which was begun in 1902 was summarized in the following report to the International Congress on Goitre in Berne, 1927:[1]]

With changing conditions of life, improvements in sanitation, protection of water-supplies, modifications in food habits and in food, the character, incidence and sequelae of 'goitre' have changed and its geographical limits appear to have widened even within the last twenty-five years. Formerly it was to be found mainly in hilly regions where persons with large pendulous goitres, and sufferers from cretinism, deaf-mutism and idiocy, were commonly encountered. To-day these grosser manifestations of the disease are less common, even in its old endemic haunts; and instead, we find smaller goitres, more widespread in their geographical distribution and more often associated with thyrotoxicosis. It is only in such localities as Himalayan India and the more remote parts of other mountainous regions where old habits and customs still prevail, and to which the amenities of modern civilization have not yet penetrated, that the classical type of endemic goitre is likely to be encountered in a state of aetiological purity. In these localities goitre-producing influences remain the same to-day as formerly; while in others they have lessened or new influences have been added to them. The constellation of causes which gives rise to goitre is not always the same, nor is the character of the disease identical, in different parts of the world.

I. TYPES OF GOITRES

I recognize two types of endemic goitre differing in their epidemiology, aetiology and pathology. The first is the classical type occurring in mountainous regions, and variously named parenchymatous goitre, adeno-parenchymatous goitre, simple hyperplastic goitre, and chronic hypertrophic goitre. The second is the diffuse colloid goitre which occurs more especially in lowland regions. The geographical limits of these two types may meet or overlap so that both may occur together in the same locality; while both may be sporadic elsewhere than in their favourite regional haunts. Intermingled with them there may be other simple, or non-toxic, goitres which are unrelated in their origin to endemic influences; of these I shall refer to one under the provisional designation of lymph-adenoid goitre (a term introduced by Williamson and

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[1] Extract from Report on the aetiology and epidemiology of endemic goitre, number 39 in Bibliography.

Pearse, 1925). 'Physiological goitre', which may occur in endemic and in non-endemic localities alike, and such terminal phases of the goitrous process as 'cystic goitre', 'fibrous goitre' and 'calcareous goitre', will not be considered. I have, therefore, to deal with three types of thyroid enlargement:

1. Parenchymatous or chronic hypertrophic goitre,
2. Diffuse colloid goitre, and,
3. Lymph-adenoid goitre.

1. *The Parenchymatous or Chronic Hypertrophic Type of Endemic Goitre*

This is the classical type of endemic goitre occurring in mountainous regions, such as the Alps and Himalayas, in association with cretinism, deaf-mutism and various forms of physical and mental deterioration. It is the type described by the older writers (Malacarme, Fodéré, Coindet, Maunoir, Iphofen, the Sardinian Commission, Saint-Lager, Baillarger, T. Kocher, H. Bircher and many others) to whom all students of endemic goitre are under deep obligation. It is, too, the type which may occur in animals living in captivity under unhygienic conditions of life: as in rats confined in unhygienic cages, or in fish reared in unhygienic tanks or ponds.

(i) PATHOLOGICAL DEFINITION

Pathologically, the condition is a true hypertrophy in which the secretory phase of the gland's activity predominates, hyperplasia is pronounced, and many new vesicles are formed. Overstrain ultimately leads to fibrosis, with the appearance in the organ of circumscribed areas or more or less solid glandular tissue (adenomata) or of colloid-containing vesicles (colloid adenomata), or of both, the amount of colloid material in the gland appearing to depend on locality. In its early stages, as in childhood, it is of the parenchymatous type; in its later stages, as in adults, it is of the adeno-parenchymatous type.

In this state of sustained hypertrophy the thyroid is constantly straining to satisfy the needs of the tissues for its active principles but just falling short of doing so; consequently, in regions where the disease exists in a state of aetiological purity, as in certain parts of Himalayan India, evidence of hypothyroidism are constantly to be seen in sufferers from it; hyperthyroidism (thyrotoxicosis) rarely or never. In the pregnant female this sequence of events may result in failure of the maternal thyroid to satisfy adequately the needs of her own tissues, and those of the developing foetus, for the gland's products; especially when some additional burden (fright, mental worry, or attacks of acute disease) is placed on its resources. As a result the foetal thyroid is unduly stimulated and congenital goitre or cretinism may arise in the offspring: a sequence of events which is equally true of experimental animals.

(ii) EPIDEMIOLOGY

This type of goitre has distinctive epidemiological features: it has its home in the high mountain ranges of the world, prevailing chiefly in their dark and narrow valleys and at altitudes which may be as high as 10,000 feet or more above sea-level. It is essentially a place disease. It prevails with different degrees of intensity in different regions and in different parts of the same region, as in villages, or even in houses, situated adjacent to one another. The intensity of the endemic is subject to fluctuation, being greater at one time than at another. It has made its appearance in places where formerly it was unknown, and has disappeared from others, or persisted in them only as isolated cases; its disappearance has sometimes been noted to follow the canalization of water supplies and improvements in sanitation. It is especially prevalent in agricultural and pastoral districts, although in many towns in endemic zones it may be rife. It is commoner in the poorer than in the richer classes, and in agricultural labourers than in those of other occupations; many persons may escape it altogether even in regions of high endemicity. It exhibits a distinct seasonal incidence, being more prone to make its first appearance in the spring and early summer months in persons not previously affected, or to undergo further enlargement at this season in persons who already suffer from it.

Epidemics may occur in susceptible individuals or in newcomers to an endemic zone, as in school children or troops, who may acquire the malady in as short a time as fifteen to thirty days. There is a marked family predisposition or hereditary tendency to the disease, the children of goitrous mothers being very prone to become goitrous; consanguinity favours its development. It is associated with congenital goitre, cretinism (myxoedematous and tetanic), deaf-mutism and idiocy; these sequelae being as much a part of the endemic as the goitre itself. Apart from congenital goitre the malady is less common in childhood than in later life, but it gradually increases in incidence as age advances attaining to its acme between the ages of 50 and 60 years. In regions of low endemicity it is much commoner in females than in males, while in regions of high endemicity its incidence in the two sexes is more equal. There is a marked tendency to spontaneous recovery in early cases, following their removal from the endemic zone; 'first attacks' rarely proceed beyond a certain point of size, the gland enlarging by a step-like series of seasonal increases; in the endemic zone itself 10 per cent or more of 'first attacks' may recover spontaneously, a figure which varies in different localities.

The endemicity of this type of goitre cannot be gauged by the prevalence of thyroid swellings in childhood. Goitre surveys confined to school children may accordingly be misleading: they commonly include the slightest swelling of the gland (in some surveys as many as 90 per cent are of this order) which may be either normal to the individual or are of a transitory character not persisting into adult life; and, they may imply a high degree of endemicity of the disease, which does not exist. The limitation of such surveys to children is as if we were to attempt the differentiation of the 'fevers' by looking only at their beginnings while ignoring their course and sequelae. A proper index of the endemicity of the classical type of endemic goitre is only afforded by: (1) the number of goitrous subjects in the general population, or in random samplings of the population at different age periods; (2) the proportion of males to females affected; (3) the number of cretinous children, deaf-mutes and idiots; (4) the number of susceptible newcomers to an endemic district who acquire the disease within a fixed time; and (5) the size and character of individual goitres. Nothing has done more to confuse the issues involved in the aetiology of the 'goitres' than the failure to recognize these criteria on which the endemicity of the classical type of the disease can alone be based.

(iii) CAUSATION

From time immemorial this type of endemic goitre has been associated in its origin with water; and even in the present state of discontent which pervades our knowledge of its causation, its relation to drinking water is generally admitted. The occurrence of the disease in fish, its experimental production in man, goats, dogs and rats, by means of substances contained in water, and outbreaks of it following the consumption of certain waters, are among the most striking proofs of the truth of this relationship. Attempts have been made, from time to time, to explain it: (a) by the excessive richness of the water in some chemical ingredient either in solution or in suspension; (b) by the poverty of the water in some chemical substance, notably iodine; and (c) by the presence in the water, either in suspension or in solution, of organic matter (notably pathogenic agents or their products). The soils with which the waters come in contact have likewise been suspected of imparting to them goitrogenous properties, or of failing to impart to them some chemical substance in sufficient amount to prevent the development of the malady.

At the present time two 'theories' have survived from amongst the many promulgated to account for this disease: the first is the iodine-deficiency theory, which sees in the poverty of iodine in the water, the soil, and the foods grown on that soil, the essential cause of goitre; the second is the infectious or toxic theory, which attributes it to some unknown pathogenic organism or to its products. Personally, I have come to believe that the truth lies in a judicious blend of both.

I propose briefly to set out the aetiological facts, as they are known to me, believing that they provide, even in their present incomplete state, a satisfactory explanation of the causation and distribution of this malady and its sequelae, and a rational means for their prevention.

(a) *Relation to Geological Formations*

I have not been able to satisfy myself that any close correlation exists between the endemicity of this disease and certain geological formations, nor that its causal agent is any inorganic substance either in solution or in suspension in drinking water. In 1848 the Sardinian Commission found that no geological formation excluded the occurrence of goitre and cretinism, but that the endemic was met with more frequently on the older than on the more recent formations. This is my opinion to-day. Nevertheless, I recognize that just as variations in the composition and quality of the food of residents in different endemic zones may impart variety to the pathological features of the goitres prevailing therein, so it may be that variations in the chemical constitution of drinking water may impart variety to the pathological characters of goitre, though not themselves the cause of the disease.

Omitting from consideration such influences as consanguinity, heredity, concomitant infections, and those which may be grouped together as 'psychic' factors, the known facts in regard to the causation of this type of goitre centre round three things: iodine, food supply and insanitary conditions of life; the last leading, as I believe, to gastro-intestinal infection possibly of a specific kind. The results of our investigations in India dealing with the relation of this type goitre to iodine are as follows:

(b) *Relation to Iodine*

(b i.) *Iodine Content of the Soil and Drinking Water*

(1) In sea-coast, sub-montane and montane localities (ex-Himalayan India) where endemic goitre is unknown, the iodine content of the soil may be very low (less than 5 parts per 10 millions), moderate in amount (25 to 45 parts per 10 millions) or high (100 to 400 parts per 10 millions). The freedom of these localities from goitre is, therefore, related to conditions of life other than the iodine content of their soils.

(2) The iodine naturally present in the soil cannot easily be washed out of it by rainfall or by floods.

(3) The richness of a soil in iodine (100 to 400 parts per 10 millions) does not preclude the presence of thyroid swellings—for the most part the so-called 'incipient goitres'—in 27·7 per cent of girls and in 11·8 per cent of boys, living at altitudes of 6,000 feet or so above sea-level, in places where endemic goitre and its sequelae (cretinism, etc.) are conspicuous by their absence in the general population. Nor does it preclude the presence of well-marked goitre in approximately 2·5 per cent of school children; these goitres being unrelated in their origin to endemic influences.

(4) In Himalayan regions where the classical type of endemic goitre exists alone, the iodine content of the soil is, in general, less than 5 parts per 10 million, although it may sometimes range between 10 and 45 parts per 10 million parts of the soil. But the disease is not always endemic in villages whose soils are as poor in iodine as those of other villages in which the endemic prevails.

(5) There is no evidence that in Himalayan India the incidence of the disease is in inverse ratio to the iodine content of the soil. In the heart of the endemic zone, as well as in the Himalayan foot-hills, two places adjacent to one another may have approximately the same amount of iodine in their soils yet goitre be endemic in the one and not in the other; or, the soils of two adjacent villages may be equally poor in iodine yet goitre be four times as prevalent in the one as in the other, although the water supply and conditions of life of the inhabitants are the same.

(6) The water supply of one place may contain appreciable amounts of iodine (300 parts per 100 billion parts of water) and yet goitre be endemic therein; the water supply of another, and adjacent place, may contain no determinable amount of iodine and yet goitre may not be endemic therein; the water supply of two places some miles apart may be the same and yet goitre be present in the one and not in the other.

(7) Drinking water containing 300 parts of iodine per 100 billion parts of water has not prevented the occurrence of the disease in endemic form in the presence of a high degree of bacteriological impurity of the water; nor has the consumption of a drinking water containing 1,200 parts of iodine per 100 billions prevented the development of goitre under experimental conditions, in young men who consumed daily large amounts of the unboiled suspended matter removed by filtration or by sedimentation from a grossly polluted, goitre-producing water.

(8) The substitution of a bacteriologically pure for a bacteriologically impure water has caused the rapid and complete disappearance of the disease from a place in which it had been endemic for seventy years, although the new water supply contained less iodine than the old.

(9) Iodine-containing salts or substitutes for salt appear to have an influence in preventing this type of endemic goitre.

(10) The disease is in general more prone to arise in iodine-poor than in iodine-rich localities in Himalayan India, though iodine-poor localities both in the hills and in the plains may be free from it.

The investigations on which these conclusions are based were carried out independently by three chemists (Dr. Newcomb, Dr. Norris and Mr. Viswanath) whose results were in general agreement. The Himalayan soils selected for study were from localities where my original investigations were made (1902–11), where the people were entirely dependent on their own agricultural produce, where there was no importation of foods from outside sources which might have increased the iodine intake of the inhabitants, where the foods consumed were the same and where—it may be expected—the iodine content of the soil, and of the water irrigating that soil, would be reflected in the food supplies. The net result of these investigations is that while a low iodine content of the soil and drinking water is, in Himalayan India, frequently associated with this type of endemic goitre this association is not invariable nor is iodine deficiency in the soil and water the essential cause of the disease.

(b ii.) *Iodine Content of the Food*

Within recent years much work has been done on this aspect of the goitre problem, notably by v. Fellenberg in Switzerland, McClendon in the United States, and Hercus and his colleagues in New Zealand. Their observations appear to indicate that a relatively low iodine intake is commonly associated with a high prevalence of goitre. This association is, however, not invariable. Few foods are poorer in iodine than Indian polished rices, which contain less than 2 parts of iodine per 100 million parts of the rice (Newcomb, 1927); yet goitre is very rare amongst the rice-eating races of India although their diet is composed mainly, and sometimes almost exclusively, of this cereal. During the course of my nutritional researches more than 1,000 pigeons have been fed exclusively on one or other of thirty varieties of Indian rice. The general effect of these rices on the thyroid gland was to cause a reduction in its size; a very occasional effect was to cause thyroid enlargement. It follows, therefore, that some goitre-producing substance other than iodine deficiency was present in those birds which developed goitre when fed on an exclusive diet of rice. This substance is either a metabolic or a bacterial toxin or a *contagium vivum*. Recently I obtained a deteriorated and bacteria-laden rice from a goitrous locality in Burma which caused large hyperplastic goitre in 12·5 per cent of birds fed exclusively upon it: a result so unusual as strongly to suggest that some positive goitre-producing agency—probably bacterial—was present in this rice and not present in others. Its iodine content was found to be no greater or no less than that of other rices causing a reduction in size of the thyroid gland (Newcomb). Its deficiency in iodine was not, therefore, the essential cause of the goitre from which certain birds suffered.

Similarly, I have found (1927) that while a minority of pigeons develop large hyperplastic goitres when fed exclusively on an iodine-poor diet of American white flour, the majority do not. The occurrence of goitre in the minority cannot, therefore, be attributed solely to iodine deficiency, but to the action of some positive agency peculiar to the affected birds.

Certain observers (1923) have reported the development within a few weeks of thyroid enlargement in rats fed on an iodine-poor diet consisting of oatmeal, patent flour, linseed meal, calcium phosphate, sodium chloride and distilled water. Recently (1926) I repeated this experiment, using large numbers of rats caged under conditions of scrupulous cleanliness; the experiment being prolonged for several months. No appreciable enlargement of the thyroid gland occurred; but out of twenty-four thyroid glands examined histologically 50 per cent had small, single or multiple, cysts in one or both lobes of the organ; the number so affected being higher the longer the animals were fed on the faulty food. This diet is a very imperfect one, causing, in my experiments, pernicious anaemia and vesical calculus.

I conclude, therefore, that the association of goitre with a low iodine content of the food is not invariable, nor is iodine deficiency the essential cause of the hyperplastic goitres which may occur in experimental animals fed exclusively on such iodine-poor and widely-used foods as white flour and rice.

(b iii.) *Relation of Iodine to Experimentally-produced Goitre in Animals*

(1) In iodine-poor localities (25 to 45 parts of iodine per 10 million parts of soil and 300 parts of iodine per 100 billion parts of the drinking water) goitre may develop spontaneously in well-fed animals confined in dirty cages. This is, perhaps, the greatest pitfall in the experimental investigation of the disease. Only the most meticulous cleanliness will prevent the spontaneous development of goitre in laboratory animals in such localities. But cleanliness will prevent it, showing that lack of cleanliness is an important factor in its causation. It can also be prevented by increasing the consumption of iodine proportionately to the unhygienic conditions of life of the animals: as by the addition of potassium iodide, cod liver oil or iodine to their food. Chlorine acts in a similar way, though its action is less certain.

(2) In iodine-rich localities (400 parts of iodine per 10 million parts of soil) goitre rarely develops spontaneously in well-fed animals confined in dirty cages. But in these circumstances the thyroid gland tends to be larger than normal. Thus: two groups of pigeons, receiving the same food and water, were confined (1926) for a period of six months one above the other in the same pen, and separated only by the netted-wire floor of the upper compartment. Through this floor the faeces of those above dropped to the wooden floor of the compartment below, which thus became impregnated with the droppings of both groups. At the end of six months the birds in the upper compartment were found to have thyroids weighing, on the average, 89 mg. per kg. of body-weight, while those in the lower had thyroids averaging 132 mg.: an increase in size of nearly 50 per cent. When the experiment was repeated, the wooden floor of the lower compartment being removed and the birds thus having access to the iodine-rich earth, no noteworthy difference in size of the thyroids in the two groups was observed although the gland was still slightly larger in the less hygienic compartment. In these circumstances the iodine-rich earth appeared to counteract in some way the contamination of the soil resulting from the droppings of the birds.

In another experiment conducted in an iodine-poor locality (1913), the soil of which contained 10 parts of iodine per 10 millions, goats were tethered for many months on the same plot of ground, which in consequence became impregnated with their alvine discharges. Some were muzzled, so that they could not nibble at the polluted earth; these were hand-fed with clean food. Others were unmuzzled, and to these their fodder was thrown on the contaminated ground. Goitre occurred among the unmuzzled goats but did not occur among the muzzled goats.

The essential cause of the thyroid enlargements which may result in these circumstances is the polluted state of the soil and of the food and water coming into contact with it. An iodine-rich soil appears to be antagonistic to the septic state of the ground which may result from the long residence of animals upon it, while an iodine-poor soil is not or not to the same extent. This may be due either to a local antiseptic action of the iodine in the soil itself or to a higher intake of iodine by animals living on an iodine-rich soil and to a similar antiseptic action in their bodies, either by direct action or through the medium of the thyroid gland.

(3) But while animals (pigeons, rats, goats, monkeys) confined in dirty cages, or living in insanitary surroundings, are less prone to develop goitre in iodine-rich than in iodine-poor localities they may, nevertheless, do so if their food be ill balanced in certain respects, although containing amounts of iodine sufficient for normal needs.

Thus: if an excess of butter or of fatty acids be added to an otherwise well-balanced food, hyperplastic goitre will arise in a proportion of the animals. This observation, which I made in 1919, has since been confirmed by Mellanby (1921) and more recently by Marine (1924). Similarly, if the food contains an excess of lime small goitres may arise, but in this case the goitre is of the colloid type (1923). In these circumstances an increased provision of iodine proportionate to the excessive ingestion of fats or of lime will prevent the occurrence of thyroid hyperplasia or the undue accumulation of colloid in the gland and the development of either type of goitre. If the fat added to the diet be cod liver oil, which contains iodine in high concentration, goitre will not arise as shown by Mellanby and subsequently confirmed by me.

Goitres resulting in experimental animals from an excess of fats in the food develop earlier and attain to greater size in dirty than in clean cages, in iodine-poor than in iodine-rich localities, and in the early spring months than other seasons.

(4) If ten-day-old tadpoles be given a diet consisting of caseinogen, white flour and green pond-weed, to which an excess of butter or of fatty acids is added, then the thyroid gland does not assume its functional responsibilities and the tadpoles fail to grow. But if iodine be added to the food in amounts proportionate to the excess of fats, then the functional activity of the gland is initiated and maintained and the animals grow normally.

These observations indicate that a sufficiency of iodine and a balanced adjustment between iodine and certain other constituents of the food are essential to the initiation and maintenance of the normal revolution of the thyroid gland's cycle of activity, viz. to normal secretion, to normal storage of colloid and to normal resorption or excretion of colloid. They show also that the amount of iodine required by the gland for this purpose depends on the composition and quality of the food and the hygienic conditions of life.

(c) *Relation to Unhygienic Conditions of Life and to Intestinal Infection*

(c i.) *The Experimental Production of Goitre in Man*

Eighteen years ago I published my first account of the experimental production of goitre in man. I had found (1904–6) on the Gilgit Fan, in the Himalayas, a series of eight adjacent villages, situated one above the other on the same unprotected water-channels, whose soils (as I now know) were equally poor in iodine, whose inhabitants were entirely dependent on their own agricultural produce, and in which the conditions of life of the people were the same, and the foods in general use the same. The classical type of endemic goitre and its sequelae prevailed intensively in these villages, to all appearances in a state of aetiological purity and uncomplicated by the presence of goitres of other types. The disease did not prevail with equal intensity in every village: there being an increase in its incidence from the first village, where 11·8 per cent of the general population were goitrous, to the last, where 45·6 per cent were goitrous. This increasing incidence was confined to adults. Goitre was not endemic in a ninth village (Barmis) which received its very pure water supply from a different source.

Whatever may have been the influences which gave rise to goitre in the first of the Gilgit villages, it was obvious that they increased in potency on the way to the last village. Their increase affected adults but not children; it had, therefore, a direct bearing on the production of the nodular (adeno-parenchymatous) goitres with which adults were afflicted. At that time the iodine content of the soil and water had not been determined, but subsequent investigations showed that the increasing incidence of adeno-parenchymatous goitre was not related to an increasing deficiency of iodine, there being the same poverty of the metalloid in the soils of all villages. It was thought that it might be related to the increasing impurity of the water supply, all other things being equal. Accordingly the sediment from the water, as it issued from the last village, or the suspended matter removed by filtration through a Berkfeld filter, was administered to young men (volunteers), newcomers to the district, aged between 18 and 22 years (with the exception of myself, who had been resident in the locality for four years and was aged at that time 30 years). The first experiment was carried out in the spring of 1906; it was repeated in the autumn of 1907, again in the spring of 1908, and in the autumn of 1909, with similar results. The subjects of the experiment were encamped on ground containing 15 parts of iodine per 10 million parts of the soil; they received a drinking water contain-taining 1,200 parts of iodine per 100 billion parts of the water, which was derived from a source (Barmis) near their camp, where goitre did not occur. All were fed alike, and the strictest discipline was maintained. In no case was this discipline infringed. Every morning and evening before the two meals of the day the men drank about 6 oz. of the suspended matter removed from the grossly polluted, goitre-producing water. In some experiments this matter had been previously boiled, in some it had not. The combined results were as follows:

(1) Of 36 young men who consumed the unboiled suspended matter 21 exhibited no change in the thyroid gland which could be detected clinically, 10 developed noticeable goitres, while 5 showed a swelling of the gland of a transitory nature.

(2) Of 31 young men who consumed the boiled suspended matter,

none showed any increase in size of the thyroid gland. The thyroid enlargement induced in this way had the following characters: It usually made its appearance between the tenth and the fifteenth day of the experiment; it showed a tendency to fluctuate in size; it reached its point of maximum size between the twenty-fifth and the thirtieth day; in some cases it disappeared during the course of the experiment; the swelling was not great nor did it progress in size after the twenty-fifth to the thirtieth day, the tendency being towards its diminution from the thirtieth day onward; it was accompanied, as a rule, with certain subjective symptoms: throbbing in the neck and feelings of fullness and discomfort. (These sensations I had an opportunity to experience in my own person since I acquired goitre under the conditions of these experiments.)

It will be noted that the characters of the experimentally-produced goitre closely simulated those of 'first attacks' of the disease as seen during epidemics or in newcomers to an endemic area in whom the malady may make its appearance as early as the fifteenth day after their arrival and disappear spontaneously in a proportion of them. This circumstance in itself would appear to preclude the possibility of iodine deficiency being the sole cause of the disease. For had it been, one would scarcely expect goitre to have appeared so soon or spontaneous recovery to have occurred, or that men consuming the boiled suspended matter would have escaped it, while 41 per cent of men similarly fed and housed but consuming the unboiled residue acquired it. It can hardly be doubted that some goitre-producing agent was contained in the suspended matter and that this agent had been destroyed by boiling. It is to be noted that water containing 1,200 parts of iodine per 100 billion did not prevent the disease in the presence of massive infection of the alimentary tract by this agent, although the water was not goitre-producing in its absence. I concluded that a *contagium vivum* was a responsible factor in the production of goitre and of the nodules which characterized it in the adult population.

It was further demonstrated, by like means in man, that filtration through a Berkfeld filter may render the water innocuous, but that neither boiling nor filtering the water may suffice to prevent the disease unless sources of infection from the soil are rigidly excluded. Water is only a vehicle for the goitre-producing agent or agents; these are rapidly destroyed in water running over non-polluted soil, or over rocks while exposed to air, sunlight and agitation.

(c ii.) *Goitre in Artificially-reared Fish*

Marine and Lenhart (1909–10), and Gaylord (1912), found that hyperplastic goitre occurred in artificially-reared trout confined in tanks located one above the other on the same water supply; the effluent from one tank flowing into the next below it in the series. The incidence of the disease increased from the first to the last tank: 3 per cent of the fish being goitrous in the first tank, 84 per cent in the last (Gaylord, 1912). This observation provided a remarkable confirmation of my own made in man four years earlier. The water supplying the tanks was not in itself goitre-producing, since 'fish which lived in the raceway above all houses and which had never been confined in the tanks maintained normal thyroids throughout their lives' (Marine and Lenhart, 1910). Those confined in the tanks were fed largely on liver: a fat-rich food, the effect of which on the thyroid gland has already been referred to. Marine and Lenhart concluded, as a result of their observations, that 'over-feeding, over-crowding and a limited water supply, were the major factors in the production of filthy, unhygienic tanks or ponds; and the insanitary, unhygienic and filthy tanks are in a very important but still unknown manner associated with the development of thyroid hyperplasia' (1910). With this conclusion I am in complete agreement. But more recently Marine (1924) has stated that 'if water is a factor in thyroid hypertrophy' [and he believes it is] 'it is due to the absence rather than the presence of some substance necessary for the prevention of thyroid enlargement' which, he considers, 'would more properly account for the malady than some virus or toxin capable of producing thyroid hyperplasia'. The absent substance he believes to be iodine. But we have just seen that if iodine be absent from the water supplying the tanks (and there is no proof that it is), then its absence is incapable of causing thyroid hyperplasia before the water reaches the tanks; we must, therefore, conclude that the causes of the hyperplasia lay in the tanks themselves and that it was not due to absence of iodine. I do not think that by the use of the word 'absence' Marine intends to imply the non-existence of iodine, but rather its relative insufficiency; if this be his meaning, then I agree that there was an insufficiency of iodine relative to the conditions of life in which the fish lived. But these conditions of life were the actual cause of the goitre, and one of them was overfeeding on a fat-rich food, another the 'filthy state' of the tanks. It can hardly be doubted that this state was due to, or resulted in, the unrestrained growth of bacterial or other pathogenic organisms. But Marine (1924) rejects the influence of pathogenic organisms, contained in the water, on the grounds that trout living in the wooden raceways (about 30 feet long) between the tanks, and in the raceway below all tanks, 'regularly recovered although living in the most polluted water'. This word 'recovered' may convey a wrong impression unless it be understood what Marine means by it. He is referring to the hyperplasia, or state of intense secretory activity of the gland, but not to the thyroid enlargement or goitre. He is, indeed, careful to point out that the fish do not recover from goitre, and in this there is the corroborative evidence of Gaylord (1912). What actually happened was that the hyperplasia ceased to progress, the colloidless, hyperplastic goitres filled up with colloid material, became 'colloid goitres' and persisted as such in the polluted water of the tail-race, where the fish were not being overfed and where they subsisted on such scraps of food as escaped from the tanks. There was no recession of the thyroid enlargement, no disappearance of newly-formed thyroid tissue, no cure of the goitre such as occurred when iodine, arsenic or perchloride of mercury was added to the water (Gaylord, 1912). All that happened was that an alteration took place in the histological character of the goitre. Further, although nine-months'-old fish, which had spent their lives in the polluted water of the tail-race, had thyroids of apparently normal structure, yet the gland was larger than normal (Marine and Lenhart, 1911). These fish, like some wild fish living in the vicinity of populated areas, were in fact the subjects of hypertrophic goitre. This in itself indicates that the polluted water, and not iodine deficiency, was the essential cause of the hypertrophy (a balanced-increase of all components of the organ), and that a supply of iodine sufficient for the turnover of the gland's cycle of activity was reaching it. But when to this effect of polluted water *per se* other goitrogenous factors, within the tanks, were added—excess of fat-rich food, over-crowding, and confinement in 'filthy' tanks—the thyroid then showed intense secretory activity and hyperplasia to the exclusion of colloid storage. Each one of these factors—polluted water, filthy tanks and over-feeding on fat-rich food—is of itself capable of causing thyroid enlargement. Their summation within the tanks gave rise to such intense epithelial proliferation as actually to suggest carcinoma. The tanks were for these fish the centre of the endemic focus of the disease, the tail-race was its periphery; and the character of the goitres in the two locations—hyperplastic in the one and hypertrophic or colloid in the other—was determined by differences in food supply and in organic pollution of the surroundings of the fish. It is not safe to assume, as Marine has done, that the degree of infectivity in these raceways was as great as that in the tanks, for the walls and bottom of the 'filthy' tanks were impregnated and coated with a material with which Gaylord subsequently produced hyperplastic goitre in rats and dogs; a material which trout, when so confined, are wont to nibble. If we look upon this material merely as a food it was, like an excess of fats, productive of thyroid hyperplasia. But it was a food composed mainly of bacteria and their products. I do not, however, need to labour this point for, as will presently be shown, other evidence has conclusively demonstrated in man himself the goitrogenous influence of bacteriologically impure water; while as Marine and Lenhart have themselves recorded, improved hygienic conditions and the provision of fresh and more abundant water supply markedly lessened the incidence of the disease in artificially-reared trout.

Marine and Lenhart, and later Gaylord, prevented thyroid hyperplasia in trout by the additional provision of iodine; while Gaylord caused its gradual recession by adding perchloride of mercury or arsenic to the water. Both of these observations I have confirmed in other animals using, however, nascent chlorine instead of perchloride of mercury (1923). It is remarkable how little attention has been paid in the literature to Gaylord's important observation regarding the effect of perchloride of mercury; the tendency ever being to extol the influence of iodine, thus restricting the problem of the causation of the disease to a too narrow field.

(c iii.) *Effect of Intestinal Antiseptics*

The therapeutic administration of intestinal antiseptics—thymol, salol, *β-napthol* and *B. bulgaricus*—to the subjects of goitre, without any change being made in their habits of life, their place of residence or their food, was shown by me (1906) to result in the cure of the disease in suitable cases. Briefly, the results were these: All the cases treated were in males; 33 were of three months' standing or less; 25 were of twelve months' standing or less; and 24 were of a year's standing or more. Of the 82 cases treated 68 were cured or so greatly benefited as to be practically so; while 14 were unaltered or only benefited to a very slight extent. The majority of the cured cases were of less than one year's standing. These results have been confirmed by Messerli (1916), and more recently by Walton (1924) who has provided the additional observation that the therapeutic combination of intestinal antiseptics and iodine may be more beneficial than either alone.

I regard these therapeutic observations as strong confirmatory evidence of the gastro-intestinal origin of this type of goitre. They show that the administration of such drugs as thymol—the action of which is a purely local one in the gut—is capable of effecting a change in the intestinal flora, in their products, or in their action at the threshold of absorption in the intestinal tract, which may bring about the disappearance of early cases of the disease.

A comparative test of the efficacy of iodine and thymol, carried out in 1905, may be referred to here: Ten young men, the subjects of recent goitres who had arrived in the endemic locality a few months previously and whose goitres were to all appearances the same, were divided into two groups of five each. All were similarly fed and housed, all had the same work to do and used the same drinking water. One group was given iodine; the other thymol. The result was the same in both groups: four cases were cured in each; showing that thymol was as efficacious as iodine. This result is similar to that obtained in trout by iodine and perchloride of mercury.

In connection with the action of intestinal antiseptics it may be mentioned that eosinophilia is usually a marked feature in early cases of this type of goitre. It may be as much as 20 per cent and is rarely less than 8 per cent. It gradually lessens with the growth of the goitre until in cases of some years' standing it is not apparent. The polymorphonuclear elements of the blood are almost invariably reduced in number and the mononuclear elements increased. These observations, which I made in 1906, have been confirmed by Marine, Miller, T. Kocher, Bauer and others. The administration of thyroid substance or of iodine restores the leucocyte count to normal (Bauer, 1912).

(c iv.) *Effect of Vaccines*

Shock doses of vaccines prepared from cultures of faecal organisms —*Bacillus coli*, *Staphylococcus aureus* and a spore-bearing organism— were next employed (1910) in the treatment of early cases of the disease; with what degree of success is shown in the accompanying illustrations [in the original article]. The type of case in which this treatment was found to be successful was of the same order as that curable by intestinal antiseptics. A like degree of success was obtained with several different vaccines; there was no specificity in their action, although it was found that some, such as one prepared from a dysentery bacillus, were not effective. An essential condition to the success of this treatment is that the vaccines should be administered in shock doses. Wilson (1925) has confirmed this observation as to the effect of shock doses of *B. coli* vaccine in causing the subsidence of goitres.

In whatever way the goitre is caused to disappear, whether by iodine, by thyroid extract, by intestinal antiseptics or by vaccines, the signs of hypothyroidism accompanying it also disappear. All act by relieving the thyroid gland of some portion of its excessive load.

(c v.) *Gaylord's Experimental Production of Goitre*

As has been mentioned, Gaylord (1912) produced goitre in dogs and in rats by the administration of the unboiled scrapings from the water-soaked wooden tanks in which goitrous fish were confined; the boiled scrapings did not produce the disease. Confirmation of my experimental production of goitre in man was thus provided.

(c vi.) *Bircher's Experimental Production of Goitre*

Bircher (1911) fed rats on cooked rice and faeces and obtained definite changes in the thyroid gland. He also produced goitre in rats by the administration of the residue left on the Berkfeld candle after filtration of goitre-producing water.

(c vii.) *Sasaki's Experimental Production of Goitre*

Sasaki's observations, carried out under the direction of Professor Wilms, in Heidelberg (1912), are as follows:

(1) Rats fed on cooked rice mixed with faeces developed moderate-sized enlargements of the thyroid gland of a diffuse form.

(2) Rats fed on cooked rice, mixed with faeces, to which potassium iodide or thyroidin was added did not develop goitre.

(3) Other toxins gave negative results when administered to rats similarly fed.

These results indicate that goitre-producing substances are contained in faeces; and that a larger provision of iodine than is provided by the food, or a larger provision of the products of the thyroid gland than is produced by the gland under certain food conditions, is required to counteract their action. They suggest also, as do my own experiments on man, Gaylord's on dogs and rats, and the curative effects of intestinal antiseptics, that these goitre-producing substances while harmless in the rectum are harmful in a situation abnormal to them where absorption is greatest: the upper alimentary tract.

(c viii.) *My Own Experimental Production of Goitre in Goats and Rats*

The results of these experiments may be summarized as follows:

(1) Goitre has been produced in goats (1910–11), under strict control, by means of water which was grossly contaminated with the faeces of goitrous persons; the incidence of the disease was 45 per cent.

(2) The oral administration to goats (1911) of living cultures of a spore-bearing organism, obtained from the faeces of a goitrous pony, caused hyperplastic changes in the thyroid gland in 57 per cent of cases. The growths were washed off the agar slopes and administered in saline. One animal in the series developed tetanic convulsions and pronounced degenerative changes in the thyroid when fed on the washed agar slopes on which this organism was grown.

(3) The administration to rats (1913) of the filtrate obtained from an emulsion of the faeces of a goitrous individual caused goitre in 100 per cent of cases. This result indicated that goitre-producing toxins are contained in faeces; an observation recently confirmed by Rush and Jones (1924). The administration of the residue left on the Berkfeld candle

after filtration of the emulsion of faeces likewise caused goitre in 100 per cent of rats. Control rats living in another compartment of the same cage, and similarly fed and watered, did not develop goitre.

(4) The administration of aerobic cultures (1913) of bacteria, grown from the faeces of goitrous persons, caused massive goitres in 30 per cent of rats. Control rats, similarly caged, fed and watered, did not develop goitre.

(5) The administration of anaerobic cultures of faecal bacteria grown from the faeces of goitrous persons caused goitres in 100 per cent of rats. Control rats, similarly caged, fed and watered, remained goitre-free. The goitres produced in this way showed a marked tendency to fibrotic change and were of small size.

(c ix.) *The Experimental Production of Congenital Goitre. Cretinism and Parathyroid Diseases (1913–14)*[1]

(1) The filtrate of an emulsion of faeces from goitrous persons was administered to a number of female rats, during a period of four and a half months, as their sole source of drinking water. A male rat was admitted to their cages from time to time. Twenty-one young were born during this period; of these 4 were eaten by their parents, 3 were cretins, 7 had congenital goitre and 7 had normal thyroids. Five animals had haemorrhagic changes in the parathyroid glands.

(2) The administration of aerobic cultures of faecal bacteria to pregnant rats caused congenital goitre in their offspring, but no disease of the parathyroids nor cretinism. When no cultures were given to a goitrous female she gave birth to young with normal thyroids, although when these cultures were given during her previous pregnancy her young had congenital goitre.

(3) The administration of anaerobic cultures of faecal bacteria to rats during a period of three and a half months caused marked congenital goitre in 52·6 per cent of their offspring, and parathyroid disease in 57·8 per cent, but no cretinism. One female subsequently gave birth to young with congenital goitre although the administration of anaerobic cultures had been discontinued during her later pregnancy.

(4) The administration to female goats of anaerobic cultures of faecal bacteria grown in 2 per cent glucose broth—10 c.c. of the culture being given to each animal daily—caused goitre in the mothers; their young being dead-born, hairless, ill developed and the subjects of congenital goitre sometimes of enormous size. Control female goats receiving no cultures and similarly fed, but kept muzzled throughout the course of

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[1] All these experiments were carried out in a goitre-free locality of which the soil contained 10 to 45 parts of iodine per 10 millions, and of which the water contained iodine in traces only.

the experiment, did not develop goitre and gave birth to young which were not goitrous. Certain control goats, similarly fed, which were unmuzzled, became goitrous but gave birth to normally developed young, some of which had very small congenital goitres which disappeared shortly after birth.

The incidence of cretinism in the offspring of goitrous rats is approximately the same as I found it to be in the offspring of goitrous women: 3 per cent.

These experiments demonstrate: (1) the action of intestinal organisms or their products in causing goitre; (2) the presence in the faeces of a goitre-producing 'toxin'[1] which is peculiarly prone to cause cretinism; and (3) the fact that by means of faecal material from goitrous persons the complete clinical expression of the 'goitre noxia'—goitre in adult animals, and congenital goitre, cretinism and parathyroid disease (the last a pathological feature of 'tetanic cretinism') in their offspring—has been elicited under experimental conditions.

(c x.) *Congenital Goitre Resulting from Thyroidectomy in the Mother*

As is well known, female dogs whose thyroids have been in great part removed prior to, or at the commencement of, pregnancy may give birth to pups with congenital goitre. This condition arises because of the accumulation in the maternal blood, consequent on thyroid insufficiency, of toxic metabolites which unduly stimulate the foetal gland. In my experiments the same result was achieved by the oral administration of bacterial toxins to pregnant animals possessed of whole thyroids. Crippling of the maternal gland can thus be produced alike by surgical means and by the toxic products of bacterial action. The crippled organ may be helped, and congenital goitre prevented, by the additional provision of iodine, probably because the processes of nutrition and of oxidation of toxic metabolites are thereby greatly facilitated. Iodine insufficiency in its relation to chronic hypertrophic goitre and its sequelae reminds one of vitamin insufficiency in its relation to beri-beri; an insufficiency of the one favours the action on the thyroid gland of certain metabolic or microbic poisons; an insufficiency of the other admits of the development of certain metabolic poisons which exercise a specific action on the heart and nervous system. The essential cause of both is a positive and not a negative agency.

The observation of Hart and Steenbock (1917) will be remembered in this connection. No 'roughage' was provided in the food of sows thereby producing poorer elimination and increased intestinal putrefaction;

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[1] This term is used in its widest sense and includes ultramicroscopic forms of pathogenic agents.

congenital goitre was present in their offspring. The provision of roughage prevented the development of congenital goitre as did the additional provision of iodine in the food.

(c xi.) *Influence of Bacterial Toxins on the Thyroid Gland*

The work of Rogers and Garnier, Torri and Crispini (1898), Sejous (1903), de Quervain (1904) and Farrant (1910) demonstrated that bacterial and other toxins were capable of stimulating the thyroid gland to increased activity and sometimes to enlargement; while Galli-Valerio (1913) isolated from the waters of the Jura Mountains an organism—the *Bacillus pseudopestis murium*—which caused goitre on injection into rats.

(c xii.) *Bacteriology of the Thyroid Gland in Goitre*

Tissue bacteriology of the thyroid gland, especially in the hands of Rosenow (1914) and more recently of Cantero (1926), has led to the isolation of organisms of streptococcal morphology in a high proportion of colloid and adenomatous goitres both of man and of dogs. Cantero has reported positive results in 94 per cent of all goitres (fifty) examined by him. Intravenous injection of the streptococcus into animals caused hyperaemia and swelling of the thyroid gland without gross lesion of other organs, the organism being afterwards recovered from the gland.

(c xiii.) *The Experimental Prevention of Goitre in Man*

There remains the final proof which I have to offer of the influence of bacterial infection, by way of the gastro-intestinal tract, in causing chronic hypertrophic goitre: In 1913 I undertook the investigation of goitre in a large school situated in an iodine-poor locality in the Himalayan foot-hills where a changing population of about 500 boys and girls resided. Goitre had at that time been endemic in the school for sixty-six years. So great was its prevalence that in some years as many as 50 per cent of the children were the subjects of noticeable goitres; while after a residence of eight years about 80 per cent became goitrous. In 1913 no less than 66 per cent of girls above the age of sixteen years were the subjects of disfiguring goitres. As a result of my investigations the conclusions were drawn: (a) that the disease was due to the pollution of the drinking water; and (b) that the provision of a pure water would cause its disappearance. Following these recommendations, made in 1914, a new piped-water was introduced in 1918 from a neighbouring town (Kasauli) with the result that within four years the endemic had disappeared; the rapidity of its decline being, of course, due largely to the non-appearance of the disease in new resident pupils. It became necessary then to determine whether its disappearance was due to an increased iodine content of the new water supply, all other factors—food, etc.—having remained unaltered. This investigation was undertaken independently by three chemists, two of whom found traces of iodine in the old supply but none in the new, while one found 300 parts per 100 billion in both. Clearly, then, the new supply did not contain more iodine than the old but less; and the cause of the disease was, as I had previously found, the bacteriological impurity of the old water supply. My prediction that a pure water supply would cause its eradication was thus fulfilled.

In this survey of the causation of the chronic hypertrophic type of endemic goitre and its sequelae, I have endeavoured to show how closely it is interwoven with the composition of the food, with the state of the gastro-intestinal tract, with the concentration of toxic metabolites in the system, and with the role of the thyroid gland and of iodine (alone or in collaboration with the thyroid) in the phenomena of nutrition and oxidation; and I have endeavoured also to show how closely the goitrogenic action of one factor is interwoven with the goitrogenic action of another. I have provided evidence of the experimental production of this type of goitre in man and in animals, and of the experimental production of its sequelae (congenital goitre and cretinism) in the latter; evidence also of its cure, and of its complete eradication from an endemic locality: all by means which indicate its casual relationship to gastro-intestinal infection. I recognize the part which iodine insufficiency may play in its causation or, more properly perhaps, the part which iodine sufficiency may play in its prevention; but the essential cause of this type of goitre is, in my opinion, a positive toxic agent derived from the gastro-intestinal tract. Gastro-intestinal infection may not in itself cause chronic hypertrophic goitre in the presence of a sufficiency of iodine, nor may an insufficiency of iodine in itself cause chronic hypertrophic goitre in the absence of gastro-intestinal infection; but when both are present the conditions for the development of this type of goitre are at their optimum. The prevention of the disease and of its sequelae, rests, therefore, on:

(1) The perfecting of sanitation.

(2) The provision of pure and protected water supplies.

(3) Efficient personal hygiene, and drainage of the gastro-intestinal tract.

(4) The use of a well-balanced food, containing a sufficiency of iodine n a natural state.

2. *The Diffuse Colloid Type of Endemic Goitre*

There is little precise knowledge as to the geographical distribution and epidemiology of this type of endemic goitre, less as to its aetiology and less still as to its biochemistry.

It is that type in which the vesicles of the thyroid are of diverse shapes and sizes, distended and distorted by the accumulation of colloid material within them, and in which evidence of antecedent epithelial hypertrophy and hyperplasia may or may not be present. Following a period of hyperplasia and its cessation colloid may accumulate in the gland in large amount. 'Colloid goitres' may arise in this way, as in artificially-reared trout and presumably also in man.

The most recent pathological research does not indicate that all colloid goitres are of the above order, nor that diffuse hyperplasia is always a necessary forerunner of 'diffuse colloid goitre'. There appears to be a variety of this disease in which colloid storage occurs, without antecedent hyperplasia, to the complete exclusion of active secretion (Williamson and Pearse, 1925). Its cause is to be sought in factors which interrupt the normal cycle of the thyroid gland's activity at the stage of colloid storage. Of these one may possibly be the ingestion of food of low iodine content or the inadequate assimilation of iodine, although there is, as yet, no satisfactory evidence that this is so. The present-day tendency is to consider 'goitres' in general too much from the narrow point of view of iodine; as might a mechanic who considered the efficiency of his engine solely from the point of view of lubrication. It is very probable that the development of diffuse colloid goitre depends on other things besides lack of iodine, and that it is related in some part at least to change in the concentration of certain ions within the cells, plasma and colloid of the gland. In this connection my own experimental work has provided the following evidence: In pigeons and rats which received an excess of lime in an otherwise well-balanced food, for a period of eight and a half months, an average increase in size of the thyroid occurred amounting to approximately 50 per cent. Thus: while the average weight of the gland in control pigeons receiving no excess of lime was 80 mg. per kg. of body-weight, that in pigeons receiving an excess of lime was 121 mg., or an increase of 51 per cent. The goitres so produced were due to the abnormal accumulation of colloid material in the vesicles of the gland, secretory activity being in abeyance. The vesicles in whole or in part of the gland were greatly distended, distorted in shape, and their walls much thinned. This effect of an excess of lime, in an otherwise well-balanced food, was prevented by increasing the amount of iodine ingested proportionately to the excess of lime. A similar effect was observed in animals following the administration of iodine in excess, but in this case secretory activity was not in abeyance; it was, likewise, counteracted by increasing the amount of lime ingested proportionately to the excess of iodine. It would seem, therefore, that a disturbance of the calcium-iodine balance in the food, and possibly in the gland itself, may bear some relation to the pathogenesis of diffuse colloid goitre. I am aware that Aschoff has obtained evidence suggesting that calcium does not increase colloid storage but that iodine makes the colloid more viscous. My own experience is, however, as stated. More recently Hewer (1927) has found evidence to suggest that a correlation exists between the H-ion concentration of the colloid and the secretory activity of the vesicular cells. If this be so it is a most important observation.

Diffuse colloid goitre exists in two forms: the acute, which is said to be associated with a high incidence in young males (Berry, 1910; Williamson, 1926); and the chronic, which is one variety of endemic goitre (Plummer, 1921; Williamson, 1926). The chronic or endemic form appears to prevail especially in the plains and at low altitudes; but few serious attempts have been made, so far as I am aware, to define its geographical distribution and to separate it aetiologically from the adeno-parenchymatous type of the disease. Of such attempts the most noteworthy is that of Levin (1924) in the Great Lake District of North America; his results show clearly the different age incidence of the two types; an observation which in itself indicates their different aetiology.

The diffuse colloid type of endemic goitre is most prevalent in children round about the age of puberty; 'it progresses with remissions for from three to five years and then regresses to barely palpable, or at least relatively small, dimensions before the twenty-fifth year. Spontaneous recovery after a relatively short course is the rule in the United States' (Plummer, 1922). 'It has a higher incidence in infancy and childhood, attains to greater size, and regresses later in life, and less completely, in those geographical areas in which it is more prevalent' (Plummer, 1922). It appears to be fairly evenly distributed in the two sexes, there being a slight preponderance in females. It is commonly associated in the same locality with Graves' Disease; but there is little statistical evidence in regard to its association with congenital goitre, deaf-mutism and idiocy—such evidence as there is suggesting that these are not essential features of the endemic. It is commonly associated with changes at the threshold of absorption in the alimentary tract; thyroxine administered by the mouth may fail to cure it; thyroxine administered intravenously rarely fails to do so (Plummer, 1922).

I have included this brief, and imperfect, account of diffuse colloid goitre mainly to emphasize that there are two types of goitre with two distinct pathological expressions in endemic zones which may be differentiated by the zone' (Williamson, 1926). My own experience has, however, been confined mainly to the parenchymatous or adeno-parenchymatous type, so that I have drawn on the work of others (Berry, de Quervain, Plummer, Levin, Williamson and Pearse) for this account of the colloid type of the disease. I will conclude this section by the following quotation from a paper by de Quervain, published in 1922: 'The histological structure of goitres varies according to the part of the country. In certain countries, especially in level regions, the diffuse colloid goitre, with and without hyperthyroidism, and the exophthalmic goitre predominate. In more mountainous countries the toxic goitre is an exception, and the nearer one approaches the centre of the endemic area, the less he meets with the colloid goitre. It is replaced by the colloid-poor, diffuse, parenchymatous goitre in childhood, and by the adenomatous-parenchymatous, nodular goitre with its degenerative forms, in adults.' It can hardly be doubted that these differences in the architecture of the endemic goitres are due to differences in altitude, soil composition, hardness of drinking water, bacteriological purity of water supplies, social and personal hygiene, and above all to differences in the quality and composition of the food supply. This brings me to the last type of goitre with which I have to deal.

3. *The Lymph-Adenoid Type of Goitre*

The existence of this type of goitre in human beings has been demonstrated by Williamson and Pearse (1925). Recently (1926) I have produced in rats a state closely resembling it. I desire to bring the experimentally produced state to the notice of the Conference mainly because of the dietetic conditions which give rise to it and of the probability that similar dietetic conditions may give rise to a similar state in man. Full details in regard to it will be found in the July (1927) issue of the *Indian Journal of Medical Research*. Time does not permit me to give more than a brief account of it here.

The basal factor in the causation of this type of goitre is a diet from which green vegetables and fruit are excluded, containing more than 60 per cent of white flour or vitamin-poor carbohydrate, 20 per cent or less of protein, and fats and inorganic salts (including iodine) in adequate amounts. It occurs in approximately 25 per cent of rats so fed and is unrelated in its origin to iodine deficiency: some animals acquiring the disease had consumed from 0·4 to 2·6 mg. of potassium iodide in their food daily, while others had received no additional iodine. The goitre arising under these conditions is more common in female than in male rats and it is of relatively small size. It is characterized in its progressive stage by intense secretory hypertrophy approaching that seen in Primary Graves' Disease, and in its retrogressive stage by exhaustion of more or less epithelia with a corresponding increase of non-secretory elements. The diet producing it is such as induces a physiologically subnormal state of the thyroid gland and of the gastro-intestinal tract; and the changes occurring in the gland are the evidence of compensatory hyperplasia in a physiologically subnormal organ or of the action of 'toxins', derived from the intestinal tract, or produced in the course of a disordered metabolism, on a physiologically subnormal organ, or of both.

In view of the almost universal use of white flour as the main staple of the dietary in Western countries, of the widespread use of vitamin-poor carbohydrates, and of the scanty use of fresh fruit and green vegetables, it seems probable that this type of goitre will be found to occur sporadically, or even in endemic proportions, among Western peoples; that it will be encountered in its progressive stage in childhood and in young women whose food contains much vitamin-poor carbohydrate, little suitable protein and less green vegetables and fruit; that its retrogressive stage will be found in older subjects whose food has had similar faults since childhood; that the subjects of its progressive stage will be prone to develop Graves' Disease following such influences as fright, mental worry, pregnancy, lactation and attacks of acute infectious disease; and that the subjects of its retrogressive stage will exhibit greater or lesser degrees of myxoedema. If these predictions should prove to be correct, then it will be found that the additional provision of iodine in the food will neither prevent nor cure this type of goitre. These matters can, however, only be decided by clinical, epidemiologica observation, and by 'goitre surveys' which are not limited to one section of the community—the children—but which take into consideration the whole population and the food habits of the individuals comprising it Outside the laboratory it will probably be found that the purity in type of this variety of goitre may commonly be obscured by the interaction with the nutritional factors which give rise to it, of other goitrogenic influences such as lack of personal and social hygiene. The varyin interactions of these influences may be expected to give variety to the characters of the 'goitre' met with in different individuals and in different localities.

It seems necessary to add that since various types of 'simple goitre may prevail in the same locality—some capable of being benefited b the prophylactic use of iodine, some not, and some may be harmed by it—the indiscriminate use of iodine as a preventative of 'goitre' is a procedure both unscientific and dangerous.

II. CONCLUSION

When I think of the permutations and combinations of the known goitre-producing influences—food deficiencies, food excesses, polluted water supplies, gastro-intestinal infection, and insanitary conditions of life—and of the possible variety of their effects on the thyroid gland, I feel that in describing only three types of 'simple goitre' I have but touched the fringe of the subject. Twenty-six years ago, at a time when our knowledge of the thyroid gland and its disorders was even more nebulous than the most pessimistic amongst us would admit it to be to-day, James Berry (1901) wrote: 'But although goitre in most cases is to be regarded as an endemic disease, caused by a definite poison, whatever that poison may be, it is impossible to assert that all cases of goitre originate from the same cause.' I can do no better than conclude on this comprehensive note. Indeed, we now know that 'goitre' is a generic term which includes a variety of diseases of diverse aetiology. Future research may, and no doubt will, further subdivide the 'simple goitres' clinically, pathologically and aetiologically. But meanwhile we have the means of preventing large numbers of them by attention to the fundamental principles of nutrition and of personal and social hygiene.

(Twenty-two sheets illustrating by charts, photographs and photomicrographs, the various matters dealt with in the Report, and affording a pictorial record of the author's work on this subject during the past twenty-five years were submitted for exhibition.)

[In 1933 a second International Conference on Goitre was held in Berne, and the following Report was submitted.]

RECENT RESEARCHES ON THE AETIOLOGY OF GOITRE[1]

The Report which I am privileged to present to you to-day relates to researches carried out since the date of the last Conference. It might well be entitled: 'Causes of Goitre as Revealed by Animal Experimentation', since it has to do mainly with observations made in animals. It is, I think, generally admitted that the physiological attributes of the thyroid gland are similar in all the higher animals; observations made in one species have, therefore, an application to those made in another, due regard being taken to different conditions of life, food, metabolism, etc., in different species. And when these observations are found to have a close similarity in all animals, from birds to monkeys, there is the greater justification for their application to man. As the Report proceeds, this justification will, I hope, become apparent.

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[1] Extract from number 66 in Bibliography.

The subjects with which I have to deal are:

(1) The biometric study of the normal thyroid gland in different species of animals: pigeons, rats, guinea-pigs, rabbits and monkeys.

(2) The statistical study of experimental data with special reference to the effects of diet on the thyroid gland.

(3) The experimental production of 'lymph-adenoid goitre'.

(4) 'Cabbage goitre'; the existence of goitrogenic agents in certain food materials, and of anti-goitrogenic agents other than iodine.

(5) The effect of insanitary condition on the thyroid gland and the interaction of this condition with faulty food in the causation of goitre.

I propose, in dealing with these matters, to confine myself to facts that have been authenticated by experimental and statistical methods of investigation. In the time at my disposal I can enter into little detail. For such detail I would refer you to the memoir entitled *The Life-line of the Thyroid Gland*, recently published by Prof. K. B. Madhava and myself, to papers from my laboratory which have appeared in the *Indian Journal of Medical Research*, and elsewhere since 1927, and to those of other investigators whose names I shall quote.

Much of our experimental work has been done in albino rats of which a large colony, averaging about 1,000 animals, is maintained in connection with our nutritional investigations. This colony has been bred from the same stock through many generations and has gradually been standardized. The rats live under conditions of perfect sanitation, in large, airy animal rooms; they are exposed daily to the sun's rays. Their food consists of whole wheat flour cakes of unleavened bread (*chapattis*) lightly smeared with fresh butter, the hard crusts of white loaves, sprouted Bengal *gram* (legume), fresh raw carrots and cabbage *ad libitum*, whole milk and water, with a small ration of fresh raw meat and bone once a week. They are killed off when approximately 2 years old. The stock is an unusually healthy one. During the past three years no case of illness, no death from natural causes, no infantile mortality has occurred in it; while in some 1,500 post-mortem examinations no macroscopical evidence of disease, apart from occasional infestation by certain entozoa, has been found. Very occasionally cases of slight enlargement of the thyroid gland are encountered in young animals: but the stock is as free from goitrous taint as any stock of animals confined in cages can well be. It may be added that all trace of thyroid enlargement is removed when the rats are given a more liberal supply of whole milk in addition to the above ration. From this disease-free stock, standard values of thyroid-weight and of the gland's proportionate size in the body, have been prepared for all ranges of body-weight between 20 and 300 gm.

I. THE MODE OF GROWTH OF THE THYROID GLAND

For an analytical study of the mode of growth of the thyroid gland, the most direct statistics are those afforded by the thyroid-weight and body-weight of a sufficient number of individuals of a given species at all ages. In order to derive a representative numerical value that would typify the growth tendency at each individual stage of bodily development, it is necessary to group together animals comprised within selected intervals of body-weight and to calculate the arithmetic mean of their thyroid-weights. The preliminary indication of the statistics so provided is that there is a relatively more rapid increase of the thyroid-weight at the earlier or lighter body-weights and, therefore, also, at the earlier ages. This mode of growth of the gland—a spurt in early life followed by a retardation in later life—is a very important phenomenon, the implications of which are apparent in connection with an organ so intimately concerned with bodily growth and development as the thyroid gland is known to be. This phenomenon has been revealed in all species of animals examined by us. It is also revealed in man as the observations of Wehefrietz (1924), Aschoff (1927), Jaffé (1930), and others, make plain.

The thyroid gland may in some circumstances be amongst the most, in others amongst the least, variable of all organs of the body with respect to weight. This variability depends on a number of factors: locality, sex, sexual activity, season, individual idiosyncrasy, sanitary condition and diet. Of these factors diet is the chief; variability being at its lowest in animals fed on a perfectly constituted diet. When the diet of any species is of diverse character, or possessed of goitrogenic quality, variability in thyroid-weight is then at its maximum.

An examination of the manner in which a representative group of thyroid-weights is distributed indicates the possibility of distinguishing universes according to the prevalence either of abnormally large or of abnormally small thyroids, by means of certain statistical criteria: the amount of positive skewness of the frequency distribution is a measure of the increasing prevalence of thyroid enlargement; the amount of negative skewness is a measure of the prevalence of abnormally small thyroids. The close association of increasing positive skewness with thyroid enlargement was established exclusively with the statistics of our own material derived from animal universes. It is of great interest, therefore, to find that Stocks (1927), analysing the frequency distribution of neck-breadths with a view to determining the prevalence of goitre amongst school children, arrived at almost identical conclusions: in normal children his frequency-distribution diagrams are normal probability curves; in children amongst whom goitre prevailed they are curves with positive skewness.

A frequency-distribution analysis is also serviceable in that, by supplying certain statistical constants, it affords information regarding the variability of the distribution. Such indices may lead to certain spurious conclusions which are discussed elsewhere (McCarrison and Madhava, 1932); but here it may be said that there is no stable biometric constant of variability associated with thyroid glands under all conditions. It is possible to obtain samples in which there are very wide ranges of variability or of uniformity among individuals. There is, therefore, great scope for individual idiosyncrasy as a factor determining the weight of the gland.

The nature of the dependence of thyroid-weight on body-weight as judged by the process of correlation indicates that in homogeneous and non-goitrous universes of animals the correlation between these two variables is high, reliable and positive; as high, for instance, as +0·9082±0·0063 in our universe of well-fed, hygienically-housed, and disease-free stock rats. In heterogeneous or goitrous universes the correlation may be low, or even negative; as, for instance, —0·2531±0·0607 in a series of goitrous rabbits (*vide infra*). As judged by the process of curve-fitting it indicates, further, that there is a non-linear or logarithmic law connecting the mutual variation of these two variables. There seems to be great justification for presuming that the mode of growth of the thyroid gland obeys the 'logarithmic law' and that many of the characteristics of thyroid enlargements are the consequences of this logarithmic law of growth.

II. THE LIFE-LINE OF THE THYROID GLAND

A serviceable form for studying the growth of an organ is to express its observed weight as a corresponding ratio of body-weight. This measure is obtained by dividing the organ-weight by the body-weight. The resultant figure—designated 'r'—is a measure of the organ's proportionate size in the body. Such a contrivance eliminates differences in body-weight in the comparison. And although it introduces certain aspects of spuriousness—inherent in any index—it will be conceded that the bulk or weight of an organ, as an organ, is relatively of less consequence than the proportionate size or share that it occupies in relation to the organism as a whole and to the general state of development of that organism. Expressed otherwise: significance attaches not so much to an absolute measure of size or weight as to the balanced adjustment of an organ with its environment. It is customary to speak of the weight or size of the thyroid gland as being such and such in certain individuals or races, or at certain ages. But such figures have little meaning since they are not expressed in terms relative to some other readily obtainable body-measurement. Accordingly, we lay emphasis on the measure which we have indicated by the symbol 'r': the proportionate size of the gland in the body as opposed to its actual weight.

This measure, 'r', may be used for the detection of abnormal distributions of thyroid sizes in any universe: positive skewness of the frequency-distribution diagrams indicating, in the same way as those of the thyroid-weights, the degree of prevalence of unusually large thyroids. For this purpose the 'r'-values yield even more precise results than the actual thyroid-weights.

If, in a normal universe, we derive the mean values of 'r' corresponding to selected intervals of body-weight, and plot these values out, we obtain a curve which brings into prominence a phenomenon of great significance, viz. the gradual increase of the 'r'-values in the earlier stages of growth, culminating in the attainment to a maximum point and thereafter turning round that point to lead into a subsequent stage of progressive diminution of these values. This property is characteristic of the standard 'r'-curve which Prof. Madhava and I have designated: 'The Life-line of the Thyroid Gland.' The logarithmic law of growth in weight of the gland, to which previous reference has been made, necessarily leads to this phenomenon in the 'r'-curve; the initial rise to a maximum and the subsequent decline. There is, in consequence, a tendency to an increasing occurrence of thyroid swellings at the earlier stages of growth of the body.

(It may be objected that the gradual decline of the 'r'-curve, coincident with progressively increasing body-weights, is a consequence of the division of the thyroid-weights by increasing denominators. It may be objected, also, that the negative correlation, usually found to exist between 'r' and body-weight, may be attributed to the process of deriving 'r'. Similarly, it may be argued that the characteristically large values of 'r' found to be associated with certain deficient diets (*vide infra*) may also be attributed to the distortions involved in the process of division by the smaller body-weights associated with impaired growth of the body consequent on the use of these diets. All these are, no doubt, sources of error or misdirection, but it is possible to safeguard against them. In the memoir referred to above these objections are answered by the mathematical method and the justification that exists, on purely theoretical grounds, for certain properties of the measure 'r' is indicated.

Concerning the last of the above objections, it may here be said that the point at issue is not the inhibition in body-weight nor the inhibition in thyroid-weight as separate phenomena, but the comparison that arises between the two *rates of* inhibition. So also in regard to the ascent of the 'r'-curve during the earlier stages of development of the body: the question here is not that both thyroid-weight and body-weight are increasing, but that the rate of growth of the one outstrips, or lags behind, the rate of growth of the other. In other words, the question is whether there is at each stage of bodily development a greater or lesser degree of elasticity of demand for one variable in terms of another.)

To enable a comprehensive estimate of the growth of the thyroid gland to be made, a means of computing the elasticity of demand for thyroid development in terms of body development was devised. It was found that the demand for thyroid growth is greater than that for growth of the body during the prepubertal and pubertal period of life; thereafter the reverse is the case. Even in a common range of body development a greater or lesser degree of importance attaches to thyroid development varying according to the conditions of life—season, sexual activity, diet and sanitary condition—under which animals live. These conditions may cause the life-line of the gland to vary as to its height, its evenness (or slope) of movement, and even as to its shape.

The life-line of the gland is higher in rats during the spring and summer months in this locality (Coonoor) than during autumn and winter; particularly is this so in males.[1] It attains to its acme of size somewhat earlier in winter than in summer. It is lower when the sexes are living apart than when in normal sexual intercourse; in the former circumstances it is of the same form and course in both sexes; in the latter it exhibits secondary rises in females but not in males. These rises have been correlated with reproductive activity.

The weights of the thyroid gland relative to the body-weights, as represented by the 'r'-values, tend to be more or less uniform in the two sexes. The significantly greater actual weight of the organ in males vanishes to a great extent when considered relative to the body-weight.

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[1] This observation is in contrast with the increase in size of the thyroid gland which is known to occur in cattle and sheep during the winter months in certain parts of the world.

Femininity has a slight, but insignificant, tendency to increase the thyroid size ('r'), this tendency being greater during the period of reproductive activity; accordingly, the life-line of the gland tends also to be higher in females. Certain diets cause the life-line to be heightened without otherwise altering its course; some lower it, while its shape and course remain the same; others increase the slope of its downward movement. Insanitary condition may, in certain circumstances, not only heighten the life-line of the gland but delay its descent or convert the normal descent into an abnormal ascent. The effects on the gland of these two paramount influences—diet and insanitary condition—will presently be considered in greater detail.

The phenomenon revealed in the life-line of the normal thyroid gland is exhibited in all species of animals—pigeons, rats, guinea-pigs, rabbits and monkeys—examined by us. We conclude, therefore, that it is exhibited also in man; as, indeed, the available data would seem to indicate. In the human thyroid we have, then, to deal with an organ located in a conspicuous position in the neck—and capable of ready examination—which normally grows more rapidly in early life than the body as a whole and often manifests this phenomenon by its visible swelling. It is not, therefore, surprising that in regions where true endemic goitre does not prevail the curve of incidence of so-called thyroid enlargement in school children should reveal the features exhibited by the normal life-line of the gland; nor that in regions where it does prevail these features should still be manifest although the effects of endemic goitrogenic influences are superimposed upon them.

This phenomenon is not peculiar to the thyroid gland. It is exhibited also by certain other organs; in greater degree by some, in lesser degree by others. But the life-line of these organs may differ from that of the thyroid gland and from each other in the precise period of bodily development at which they attain to their maximum weight relative to that of the body. Thus, the thyroid and adrenal glands attain to their acme of size about the same time—just prior to puberty; the testicles attain to their acme after puberty and with the onset of reproductive activity. Without a knowledge of this phenomenon any of these organs might be suspected of abnormal enlargement when, in truth, they are but obeying the natural or physiological modes of their growth. A meticulous measurement of the adrenal glands, if this were possible in the human subject, would probably reveal a similar incidence of enlargements in normal school children to that revealed by an equally meticulous measurement of the thyroid gland.

The phenomenon is also exhibited in certain animal universes wherein goitre has been produced under experimental conditions: as in rabbits fed on an exclusive diet of cabbage. Provided the goitres so produced be of a type representing the physiological response of efficient thyroids to the goitrogenic stimulus, the features of the gland's life-line in the goitrous universe are identical, as to shape and course, with those in a non-goitrous universe of the same species: the line rises relatively rapidly when body growth and development are proceeding rapidly and falls gradually as these processes tend towards completion. But it differs as to height in the two universes; being higher in the goitrous than in the non-goitrous one. If, however, the goitrogenic influence be of a kind which induces retrograde changes in the gland or if the gland be physiologically inefficient then the life-line will be disturbed, its descent delayed or even converted into an ascent. It is imperative, therefore, to arrive at some criterion whereby we can judge of the normal height of the gland's life-line and of the departure of the organ from a normal size in individual cases. For this purpose it is necessary to establish the normal mean size ('r') of the gland for individuals included in certain categories of body-weight; categories covering the whole span of life. It is obvious that if we adopt a low standard of departure from the normal means—such, for instance, as 0·5 times the standard deviation from these means—we will find a high incidence of thyroid swellings which, without a knowledge of the above phenomenon, may be regarded as abnormal when in reality little or no abnormality may exist. Applying this low criterion to an almost wholly normal universe of rats, an incidence curve of thyroid swellings was arrived at which reproduced the features of the incidence curve of 'goitre' obtained in some surveys in school children. Briefly, it may be stated that the criterion to which our studies have led us is one represented by the formula: mean $\text{'r'} + 2{\cdot}5\delta$; for which justification is forthcoming from the theory of normal probability. Glands yielding values in excess of the figure given by this formula are abnormally large or goitrous; they are examples of 'true goitre'. Those yielding values that are not in excess of this figure are not of abnormal size, however else they may be abnormal structurally. Applying this higher, and truer, criterion to a universe of 350 hygienically-housed and well-fed stock rats, six cases of thyroid enlargement ('true goitre') were revealed; applying it to another universe of 246 rats, similarly housed but whose stock diet was enriched with a more liberal supply of whole milk, no cases of thyroid enlargement were revealed—both findings being confirmed at post-mortem examination of the 596 animals. Thus macroscopical and microscopical evidence support the accuracy of the higher criterion, which, on general statistical grounds, is the most suitable one to employ.

III. GOITRE SURVEYS

In the memoir, referred to above, reference is made to the practice of conducting goitre surveys in school children by the method of visual examination, and to the lack of uniformity in standards of judgement and in the classification of results. In this connection our studies have led us to the following conclusions: (1) for accurate goitre surveys it is desirable to have not only a qualitative measure of the thyroid—such as neck-breadth (Stocks, 1927)—but another associated statural measure, in order to express the former as a proportionate value of the latter: i.e. of a developmental aspect of the body. The thyroid gland is a living organ associated with the development of the body and not a chronological event; it requires, therefore, to be set against some functional measure of the body rather than against age. Normal standards of thyroid size ('r'), whereby departures from the normal size can be estimated, should be derived in some such way; (2) minute subdivision into grades of thyroid enlargement is not successful—particularly with the methods of visual examination, commonly employed—nor is it necessary when the point of view of nation-wide statistics is distinguished from an individual's complaint. It has always happened that the smallest grade of thyroid enlargement bears to the total of all grades of enlargement, whatever be the actual criteria employed by different surveyors, a fraction of over 50 per cent, amounting in some instances even to 85 per cent. This smallest grade of enlargement has often little or no title to be regarded as pathological; (3) a particular example was worked out with the results of a certain survey in school children in the United States of America (wherein a very elaborate scheme of classification of thyroid enlargements was employed) to exhibit the changes introduced in them when they are redistributed according to one or other of the schemes of classification employed in rats. It was shown that the number of school children that corresponded to those of 'true goitre' in our stock rats (6, or 1·7 per cent) were no more than 696 among the 47,493 children under examination, or an incidence of 'true goitre' of only 1·46 per cent; (4) rates of incidence in aggregate groups of school children are naturally influenced by the caution or freedom with which surveyors under-emphasize or over-emphasize an enlargement of the gland. But when the results of separate surveys are expressed in terms of a common denominator, that is to say, when the aggregate incidence in each universe is taken as a common number—say, 100—the incidence curves at individual ages are in very great similarity amongst themselves, and reveal a remarkable resemblance also to that in an almost wholly goitre-free universe of rats. Accordingly, we conclude that some of these universes of school children were, in truth, as normal with respect to the size of the thyroid gland as was this universe of rats, wherein the rarity of true goitre was established both by biometric and morbid anatomical means. If 'childhood goitre' is understood to be a condition occurring with increasing frequency as age in childhood advances, then we notice that this phenomenon tends to manifest itself as an inverted parabola, rising with the advance in age up to puberty and thereafter declining until a low level (amounting almost to disappearance) is reached after puberty; a phenomenon similar to that exhibited by the life-line of the normal thyroid gland.

The incidence of goitre in school children is not a true criterion of the endemicity of the disease. Indeed, many of the so-called 'childhood goitres' are not a diseased state of the thyroid gland at all, but the normal expression of the organ's place in relation to the growth and development of the children concerned. If this be admitted, a great source of confusion will have been removed in regard to the aetiology of 'endemic goitre' and a division made between the physiological and the pathological. For even if we adopt a considerably lower criterion (mean 'r'$+1{\cdot}0\delta$) of thyroid enlargement than that (mean 'r'$+2{\cdot}5\delta$) given above, then by this lower criterion approximately 50 per cent of cases, now commonly included as examples of 'thyroid enlargement' in school children, will be eliminated. We will not, I think, go far wrong if we regard thyroid glands whose size is greater than the figure yielded by the lower criterion ('r'$+1{\cdot}0\delta$) but less than that yielded by the higher ('r'$+2{\cdot}5\delta$) as examples of 'physiological swellings', and those which exceed the latter as examples of 'true goitre'. Some such division as this is called for if the existing confusion is to be avoided.

IV. MODIFICATION OF THE ACTUAL AND RELATIVE THYROID-WEIGHT BY DIET

It has been shown above that the positive skewness of the frequency-distribution diagrams of thyroid-weights or sizes is a measure of the prevalence of unusually large glands. In animals fed on well-balanced diets these diagrams are either normal probability curves or curves exhibiting slight positive skewness. In those fed on certain deficient and ill-balanced diets the frequency distribution diagrams exhibit negative skewness owing to the presence of a large number of unusually small thyroids; yet, in such deficiently-fed universes cases of 'true goitre' may, as will presently appear, be encountered in some individuals. It has been shown, also, that in perfectly-fed universes the size of the thyroid gland does not exceed a certain limit and that goitre is absent from them or very rare. Further, perfect nutrition eliminates individual idiosyncrasy, to a great extent, as a factor in the causation of variation in thyroid-weight or size. The important rule has thus emerged that *the more perfect the diet the more normal is the frequency distribution diagram of thyroid-weights or sizes, the more stable is the thyroid gland in point of size, and the less likely is goitre to occur.*

An example of the extent to which the size ('r') of the thyroid gland may differ in rat universes derived from the same standardized stock, when fed on certain selected diets, is afforded in the following table:

Diets	*'r'-value (Weight in mg. per 100 gm. of Body-weight)*	*Standard Deviation of 'r'*	*Co-efficient of Variation of 'r'*	*Percentage Incidence of True Goitre*[1]
1. Complete synthetic diet (iodine added as KI)	6·63±0·37	1·27	19·0	0
2. Vegetarian diet with 3 c.c. of whole milk per rat	6·94±0·12	1·20	17·3	0
3. Ditto, without milk	7·13±0·18	1·71	23·9	0
4. Synthetic diet as in 1, but containing 40 to 80% of animal protein	8·05±0·16	1·96	24·4	0
5. Stock diet with additional milk	8·18±0·12	1·90	23·2	0
6. Synthetic diet as in 1, but containing little or no animal protein	8·10±0·26	2·62	32·3	2
7. Cabbage-oatmeal-and-wheat diet (60 : 20 : 20)	8·45±0·25	1·87	22·0	2
8. Stock diet	9·76±0·11	2·15	22·0	2
9. Cabbage-sorghum-and-wheat diet (60 : 20 : 20)	10·38±0·33	2·46	24·0	7

These diets are, with one exception, arranged in order of the thyroid gland's magnitude and in increasing order of goitrogenic potency. The exception is provided by the stock diet (No. 5) to which a more liberal supply of milk was added. Milk rendered the universe free from cases of true goitre, it reduced the aggregate thyroid-weight and it maintained the distribution of thyroid sizes in a more uniform manner.

These effects are not so conclusively brought out in the presence of a well-balanced diet, such as the stock diet is, but in the presence of a diet deficient in vitamin-A-bearing ingredients, and ill-balanced in other

[1] By 'true goitre' is meant an increase in the 'r'-value over the normal mean by more than 2·5 times the standard deviation from that mean.

respects, the stabilizing and anti-goitrogenic action of milk (Coonoor) is quite remarkable.

In certain circumstances whole milk may have an effect the reverse of that here noted. Thus, many years ago it was observed by Steenbock that sows gave birth to goitrous young when their diet was rich in whole milk, but not when it contained the same amount of skimmed milk. An explanation of this observation is probably to be found in the fact that butter has different effects on the thyroid gland depending on the composition and quality of the diet to which it is added. When added to a diet deficient in fat and fat-soluble vitamins, it counteracts the tendency to increased thyroid size, as well as the tendency to true goitre, induced by the deficient diet; when added in excess of requirements to a complete diet it has a definite goitrogenic action (McCarrison, 1920; Mellanby, 1921). This action is counteracted by the additional provision of iodine. There is, as I pointed out in 1921, a fat/iodine balance in nutrition; disturbance of which has a disturbing effect on the thyroid gland. In this connection the observations of Abelin and his collaborators (1928) are of great interest. They find that an antagonism exists between thyroid activity and the metabolism of fats: an excess of thyroid hormone inhibits the anabolism of fats and, inversely, the enrichment of the organism in fats diminishes the activity of the thyroid hormone.

A lack of vitamin-A-bearing ingredients (milk, green vegetables, carrots, etc.) in the diet is one of the main factors concerned in the production of thyroid-weights which are increased relative to that of the body. A statistical explanation of this finding is the disparity in the adjustment of the thyroid-weight to body-weight as a result of subsistence on diets having this fault. The increase in size of the thyroid gland that is caused by them is of a persistent kind; the amount of persistence being proportional to the degree of impairment of body-weight. In universes of albino rats the life-line of the gland tended to lose its normal characters and to persist at a relatively high level after the period which corresponds in these animals to puberty in human beings. Such diets tend to render the thyroid gland physiologically inefficient and cases of true goitre are prone to arise in consequence of their use.

Radiostoleum (which contains both vitamin A and vitamin D) was found to have exercised a definite, though slight, action in increasing the weight of the thyroid relative to that of the body, when it formed the source of these vitamins in an otherwise 'complete' diet, and when added to diets ill-balanced with respect to calcium and phosphorus. This observation falls into line with that of Stiner (1933) who reports the production of thyroid enlargements in guinea-pigs fed for long periods on irradiated pasteurized milk. I have not found that deprivation of sunlight increased, nor that exposure to the direct rays of the tropical sun diminished, the incidence of goitre in albino rats fed on a goitre-producing diet. This observation is in conformity with those of Krauss and Munro (1930), and of v. Fellenberg (1931), demonstrating the lack of anti-goitrogenic action of ultra-violet radiation; and in conformity also with that of Thompson (1931) regarding the failure of vitamin D to prevent goitre in rats fed on a rachitogenic diet containing a high proportion of calcium carbonate. Ultra-violet light does not, however, appear to be without effect on the thyroid gland: it is reported by Rosenkranz (1931) to cause the follicles of the gland in rabbits and cattle to become distended with colloid.

A scorbutic diet (deficiency of vitamin C), consisting of crushed oats and autoclaved milk, causes a significant increase in the proportionate size ('r') of the thyroid gland in guinea-pigs and actual goitre in some cases (McCarrison, 1919). This increase in size is accompanied with an increased concentration of iodine (Sankaran, 1931), and a greater content of colloid material, in the gland. The pH of the organ is lessened; averaging 6·90, as compared with 7·04 in well-fed controls. This tendency to increased acidity is also observed in the blood and bile but not in other organs. The adrenal glands are enlarged; their adrenalin content is reduced; and haemorrhagic areas may be present in the cortex (McCarrison, 1919). The urine is highly acid.

It has recently been claimed by Svirbely and Szent-Györgyi (1932) that vitamin C is a single substance identical with hexuronic acid. (Szent-Györgyi has now (1933) suggested the name ascorbic acid ($C_6H_8O_6$) for the substance thought to be identical with vitamin C.) Further evidence —based on the silver-nitrate-staining capacity of adrenal glands taken from normal and scorbutic guinea-pigs—of the identity of this substance with vitamin C has recently been advanced by Moore and Ray (1933). If this be so, then a deficiency of hexuronic acid in the diet tends to the production of goitre in guinea-pigs, with an increase in the iodine content of the enlarged gland. Having regard to the biological activity of hexuronic acid, this observation may be one of profound significance:

'A characteristic property of hexuronic acid is its behaviour towards iodine. Two atoms of iodine are taken up in aqueous solution (neutral or acid) with formation of two molecules of hydrogen iodine. We find that this is due to oxidation at a double bond. The intervention of water is essential and the product, which is not a di-iodide, can be reduced to hexuronic acid. Regeneration of hexuronic acid occurs only when the aqueous solution of the oxidation product is reduced, for example, by evaporation in the presence of hydrogen iodide.

'The biological activity of the acid is probably due to this double function of oxidation and reduction which, unique among purely carbon compounds, is reminiscent of glutathione. . . . We have examined (with R. W. Herbert) the absorption spectrum of de-citrated lemon juice and have estimated that the hexuronic-acid content corresponds with the recorded evaluation of the antis-corbutic activity of isolated hexuronic acid' (Cox, Hirst and Reynold, 1932).

Diets in which several vitamin deficiencies are combined are more potent in favouring the development of goitre than those deficient in a single vitamin. Such diets, when made up of food materials in common use by man, are almost invariably faulty in other regards and are probably rendered more so by culinary procedures. Deficiency of suitable protein, or of certain mineral elements or, it may be, of certain enzymes, and excess of carbohydrates are among the common faults of such vitamin-deficient diets. These faults contribute their share to the general effect of the diets on the thyroid gland.

(It is preferable to speak of 'deficiency of vitamin-bearing food materials' in the diet rather than of deficiency of the vitamins themselves. For although the effects of such deficiency may be due mainly to the vitamin deficiency yet there is the possibility that they may be related also to deficiency of other elements and complexes, known and unknown, with which the vitamins are associated in natural, and living, foodstuffs (McCarrison, 1931).)

A high proportion of animal protein in an otherwise complete synthetic diet, containing iodine in the form of potassium iodide, did not cause the weight of the thyroid gland in albino rats to be increased over that of rats fed on a well-constituted stock diet. On the contrary, the gland was significantly smaller than normal; an observation recalling those of Watson (1912), Degener (1922) and Tsuji (1922). It is to be noted, however, that the mean weight of the organ relative to that of the body was, in the aggregate, higher in rats fed on high-protein diets than in others fed on purely vegetarian diets; the latter being well balanced with respect to their content of proteins, fats and carbohydrates (1 : 0·6 : 8·3). Compared with such vegetarian diets, those rich in animal protein did cause the thyroid gland to be larger. In this connection the observation of Carrel (1926) may be recalled: he found that the growth of colonies of thyroid epithelium *in vitro* was greatly stimulated by peptone (Witte). It is known also that the subcutaneous injection of tyramine produces hyperplasia of the thyroid.

There is a definite tendency for the weight of the thyroid gland relative to that of the body to increase when the diet, besides being low in vitamin-A-bearing ingredients, is also low in protein; this tendency is due to the not infrequent occurrence of actual goitre in the rats so fed.

The observations of Kirsch (1926) and Stefko (1931) in malnourished children are noteworthy in this connection.

Inanition *per se* causes a marked reduction both in the actual weight and in the size of the thyroid gland. Thus, in a series of starved pigeons (McCarrison, 1919) whose average body-weight at death was 206 gm., the thyroid size was 7·7 mg. as compared with 10·7 in well-fed controls of the same body-weight (see also Jackson (1916) and Rabinovitch (1929)).

Certain diets, composed solely of deteriorated rice or of autoclaved rice or of American white flour, were found to enhance the weight of the thyroid relative to that of the body; other rices—parboiled, milled, washed and unwashed—were less potent in this regard. Although, in general, the thyroid gland was below normal size, a small proportion of pigeons fed on these diets developed true goitre. Rice and white flour are of low iodine content, yet it was only in a minority of birds fed upon them that goitre occurred. In a recent experiment (pigeons) it was found that the addition of millet to a diet of washed, polished rice caused a significant increase in the incidence of true goitre although its addition more than doubled the iodine content of the food mixture. The property exhibited by autoclaved rice to enhance the thyroid size was shown (in monkeys) to have been counteracted in progressively increasing degree by the addition to it of butter, of butter and onions, and of butter, onions and fruit; that is to say, by progressive improvement in the balance of the diet.

It was shown in regard to goitres arising in animals fed on certain low-protein diets deficient in vitamin-A-bearing food materials, or on certain rice diets, or on diets composed mainly of white flour—in all of which the faults are multiple—that dietetic factors alone were not sufficient to account for the occurrence of goitre and that it was necessary to postulate the existence of some other goitrogenic agent—possibly a *contagium vivum* or noxa—not examined by us under control. Nevertheless, the provision of a perfectly constituted diet afforded the animals complete protection against this hypothetical agent; so far, that is to say, as the occurrence of thyroid enlargement was concerned.

V. LYMPH-ADENOID GOITRE

A goitrous condition to which the above term—introduced by Williamson and Pearse (1925)—has been applied, was produced under experimental conditions in albino rats. It is identical in histological appearances with the lymph-adenoid goitre described by these authors in human beings. They define it as 'the hypertrophic reaction of a

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physiologically inefficient organ with which there occurs a preponderance of lymphocytic aggregates, fibrosis, and a peculiar atrophy of the parenchyma. The condition can be focal and non-goitrous.' This definition exactly describes the malady as I have seen it in rats; and its recognition introduces the important consideration of the relation between the state of physiological efficiency of the thyroid gland and the genesis of goitre. We are accustomed to think of the thyroid as always capable of responding to goitrogenic influences in a certain way, namely, by undergoing hyperplasia. But it may be rendered—as by faulty nutrition—incapable, or only partially capable, of such efficient response; then the appearances presented by it, as a result of subjection to goitrogenic influences, may differ from those presented by one that is physiologically more efficient. Accordingly, it is necessary to think both of the gland's capacity of response to such influences and of the nature and specific effect of the influences themselves.

Lymph-adenoid goitre has been observed in rats fed on synthetic diets whose main fault was one of vitamin deficiency; such, for instance, as a diet composed of white flour or starch, olive oil, meat residue and salt mixture containing 0·45 per cent of potassium iodide. It has been observed also in rats fed on a diet composed of white bread, dried yeast, lime and iodine-water. It is obvious, therefore, that it can occur despite the adequate ingestion of iodine. It has never been observed in rats fed on the former diet when the vitamin deficiency was corrected by the addition of cod liver oil and yeast. Nor has it been observed in those fed on well-constituted diets containing an abundance of roughage, fresh vegetable foods and milk. The incidence of the condition rarely exceeds 10 to 15 per cent, though in one experiment it was as high as 41 per cent (McCarrison, 1930). Its occurrence is haphazard; that is to say, a repeat experiment may reveal no examples of it. Deficiency of vitamin A appears to be the chief dietetic cause of its occurrence; but it is not the ultimate cause. It is related in its origin to some peculiarity, constitutional, toxic or microbic, of the individuals affected by it. The diets associated with its occurrence have definite effects on the thyroid gland. Of these the formation of keratinization cysts is the most constant; colloid accumulation—amounting sometimes to the production of small colloid goitres—comes next in order of constancy; the aggregation of lymphocytes, is the least constant feature. Spence (1932), while confirming the first two of these findings and the production of goitre in rats by the use of my experimental diets, containing iodine in large amount, failed in his series to find examples of lymph-adenoid goitre: a failure due possibly to differences in quality of the ingredients of the diets, as between those available in Coonoor and those available in London, or, more probably still, to differences in susceptibility or in bacterial flora of the rats in the two localities. It seems certain that these effects on the gland are the consequences of vitamin-A deficiency, and that the epithelium of the thyroid is affected similarly to other epithelia throughout the body by this deficiency. The lymphocytic infiltration appears to be related to the epithelial degeneration, and to be comparable to that which may occur in the upper part of the respiratory tract of rats fed on these deficient diets: in this situation the infiltration may reach such proportions as to cause adenoid-like projections which greatly reduce the lumen of the trachea. Distension of the thyroid vesicles with colloid, and their frequent distortion, may accompany this condition; an observation which recalls the finding of Breitner (1927) that the artificial restriction of the lumen of the trachea in the rat induces a state of excessive colloid accumulation in the thyroid gland. A low-grade inflammatory process is involved in the production of these adenoid-like growths in the trachea; and so it would seem to be in regard to the production of lymph-adenoid goitre. Whatever be the ultimate cause of this type of goitre in rats, it is clear that a perfectly constituted diet affords them complete protection against it.

(Attention may here be drawn to the importance of caging rats in roomy, well-ventilated cages in which free movement and exercise is possible. Without these amenities the thyroid gland tends to be larger than normal.)

VI. LIME EXCESS AND GOITRE

The frequent association of goitre with limestone rocks and with drinking water rich in lime has been noted from the earliest times. Nearly one hundred years ago M'Clelland (1835) drew attention to it in certain parts of sub-Himalayan India. It is now well known that this association is not constant; and, in consequence of its inconstancy there has, perhaps, been a tendency to minimize the important part which lime excess may play both in causing goitre and in modifying the histological features of the goitrous gland. So far as I am aware, the first experimental proof of the goitrogenic action of lime was afforded by Repin (1911), and subsequently by McCarrison (1925), and by Tanabe (1925). The more recent work of Krauss and Munro (1930), Hellwig (1931), Juanita Thompson (1932), McCarrison and Madhava (1932) and Harold Levine (1932) has added to our knowledge of the relationship which excess of lime in the food may bear to goitre. It now appears to be bound up with a relative deficiency of iodine or of phosphates.

In my own experience it was found that the addition of an excess of calcium carbonate to a diet of mixed grains caused a significant increase in size of the thyroid gland in pigeons, the mean 'r'-value in controls, to which no lime was given, being 80 mg. per 1,000 gm. of body-weight and 121 mg. in those that received the lime. This increase in size of the gland was found to be prevented by the additional provision of iodine; the mean 'r'-value being 82 mg. in birds that received both lime and iodine. The enlargement of the gland was associated with the accumulation of colloid material in the follicles; an accumulation which was prevented by the additional provision of iodine. The small 'colloid goitres' so produced were of lower pH than normal; the tendency to increased acidity being observed also in other organs of the body, while the blood was slightly more alkaline than normal.

(The state of the thyroid gland's activity appears to be related to the concentration of H-ions within the organ; colloid being accumulated when the gland is more acid and dispersed when it is more alkaline. Hewer (1927), also, has found evidence suggesting that a correlation exists between the H-ion concentration in the colloid and the activity of the vesicular cells.)

While a diet high in calcium and low in iodine may favour goitre production, so also may a diet high in iodine and low in calcium. Thus, in the experiment quoted above, the mean 'r'-value of the thyroid gland of birds that received the same amount of iodine, but without the addition of lime, was 129 mg.: a size as great as that in birds that received lime but no additional iodine. Disturbance of calcium/iodine balance in either direction is, therefore, a factor of importance in the genesis of goitre. It is to be noted that in both circumstances—excess of lime or excess of iodine—the resultant thyroid enlargements were, in pigeons, of the colloid type.

An excess of lime in a diet low in phosphates, such as one composed largely or mainly of white bread, is likewise favourable to goitre production in albino rats. This was found to be due to a relative deficiency of phosphates consequent on the lime excess. It was counteracted, to a great extent, by the addition of suitable amounts of sodium phosphate. The diet referred to here was deficient also in vitamin-bearing ingredients and in suitable protein. Cases of goitre were occasionally encountered even after the calcium/phosphorus imbalance had been corrected; but when the other defects of the diet were also corrected, as by the addition of suitable amounts of milk, the thyroid enlargement was wholly prevented. This observation again brings into prominence the importance of vitamin and protein deficiency in favouring the genesis of goitre.

Thyroid enlargement of the hyperplastic type has been observed by

Krauss and Munro (1930), Juanita Thompson (1932) and Harold Levine (1932) in rats fed on the Steenbock rachitogenic diet. The enlargement is unrelated to deficiency of vitamin D. It is due to an excess of lime in association with a relative deficiency of iodine; the hyperplasia being the greater the greater the disproportion between the two elements. There appears to be a quantitative relationship between them: a definite amount of iodine being needed in proportion to the amount of lime present in the diet.

Two types of goitre have thus been observed in association with calcium excess in the food: the colloid type in pigeons and the hyperplastic type in rats. Both are preventable by increasing the iodine content of the food proportionately to the calcium excess. Whether or not the two types are due to metabolic differences in the two species or to a different concatenation of food constituents or to locality or altitude I do not know.

These observations emphasize the importance both of calcium/iodine and of calcium/phosphorus imbalance in relation to goitre production. They show, also, that mineral imbalance may interact with vitamin and protein deficiency in causing thyroid disorder. In the prophylaxis of goitre it is, therefore, essential to correct any such imbalance; as by the use of an iodized 'salt mixture' (see also Van Wendt, 1929), together with a sufficiency of food materials containing suitable protein and vitamins.

Other mineral substances, stated to have a goitrogenic action, are fluorides (Cristiani, 1930) and radium (Repin, 1908).

VII. EFFECT OF IODINE ON THYROID TISSUE *IN VITRO*

Recently, an attempt was made in my laboratory to ascertain the effect of iodine on thyroid tissue grown *in vitro*. The culture medium employed was hen plasma 50 parts, embryo extract 25 parts and Tyrode solution 25 parts. The coverslip method of culture was used. (The technical part of this work was carried out by my assistant, Dr. G. Sankaran.) Iodine was added to the medium in the form of sodium iodine. The cultures were examined at six-hourly intervals and their rate of growth recorded in the usual way (Ephrussi, 1932).

Briefly, our results were these:

(1) The addition of 12·5 μg. of iodine per 100 c.c. of the culture medium had little effect either on the rate of growth or on the metabolism of the growing cells. If anything, the effect was slightly stimulating.

(2) The addition of 25·0 μg. had a pronounced stimulating effect on

growth. It also increased the rate of metabolism of the growing cells, as evidenced by the rapidity with which digestion of the medium, and resultant vacuole-formation occurred.

(3) The addition of 50·0 μg. increased the rate of metabolism, but had only a slight stimulating effect on the rate of growth. The life of the cells was shortened proportionately to the increased rate of metabolism; growth ceasing, and cellular disintegration occurring, ten hours earlier than in the corresponding controls.

(Bromine (100 μg.) had a similar action.)

(4) The addition of 100·0 μg. greatly enhanced the rate of metabolism and halved the duration of life of the cells; growth ceasing at the fortieth hour instead of at about the eightieth hour as in controls. During the forty hours of their life the rate of growth was equal to that in the corresponding controls.

The effect of these higher concentrations calls to mind that of the administration of iodine to tadpoles: in these larvae metamorphosis is hastened while growth is retarded.

Some evidence was obtained which suggests that the stimulating effect of iodine may not be peculiar to thyroid tissue. A similar, but less marked, effect was observed in cultures of fibroblasts. But as this work is still in progress, no definite statement can, at present, be made in regard to it.

The above observations had been made when the recent work of Demuth (1932) came to my notice. He found that the growth of thyroid cells was markedly greater in the plasma of iodized fowls than in that of non-iodized fowls.

These results confirm those of Leo Loeb (1920–9), Rabinovitch (1928, 1929) and others, demonstrating that small doses of iodine, administered as potassium iodide, caused marked stimulation of the thyroid gland (guinea-pigs), as evidenced by numerous nuclear divisions. This stimulation is subsequently followed by colloid accumulation. According to Ebeling (1925) colloid accumulation does not occur in cultures of thyroid epithelium *in vitro* so long as the cells are multiplying; growth must be slowed down before such accumulation can occur (Ephrussi, 1932).

I find it difficult to reconcile such observations as these with the view that deficiency of iodine can also stimulate the thyroid cells to multiply (hyperplasia).

VIII. IODINE AND GOITRE

The results to be recorded under this heading are derived from a statistical study of the data provided by: (a) certain surveys of goitre in school children; (b) some of my own experiments in animals; (c) the estimates of iodine in food and water; and (d) the iodine content of the urine of goitrous and non-goitrous persons resident *in the same endemic locality*. They may be summarized as follows:

(1) The hyperbolic relation between goitre prevalence in school children and the level of soil-iodine, suspected by Hercus, Benson and Carter (1925) in New Zealand, was confirmed by our statistical scrutiny of the data collected by them in twenty-seven districts. But a statistical curve-fitting gave us a different numerical relation though of the same category. The implication of this difference is to alter the limiting value of incidence from 6 per cent, as given by these observers, to 10·5 per cent. Another implication of the algebraic relation is that, in New Zealand, goitre-incidence is never *nil* whatever may be the level of soil iodine.

Certain districts in New Zealand were strikingly at variance with the inverse relation between soil iodine and goitre-incidence. The association of goitre with a low iodine content of the soil is, therefore, not invariable (see also Ucko, 1932).

(2) Whatever be the level of soil iodine the incidence of 'thyroid enlargement' in school children gradually rises up to about the age of 13 years and thereafter falls; the incidence-curve being higher the lower the iodine content of the soil. After the age of 13 the drop in the incidence-curve is as marked, or more marked, in localities where the iodine content of the soil is lowest as in those where it is higher (Shore and Andrew's data, 1929).

(3) The iodine content of the soil is approximately the same in the neighbourhood of Coonoor (Nilgiri Hills, S. India) as in certain parts of New Zealand; yet goitre is not endemic in the former locality while it is endemic in the latter.

(4) It would seem that after the physiological stress of puberty is passed the inverse law, relating goitre to iodine deficiency in the soil, does not apply. From data, obtained in the United States of America, it was apparent that a high incidence of 'thyroid enlargement' in school children was not necessarily associated with a high incidence of goitre in young adults.

(5) No correlation could be established between the iodine content of the drinking water in the villages of Gilgit, Himalaya (McCarrison, 1906), and the incidence of goitre in the villagers (McCarrison *et al.*, 1927).

(In this connection reference may be made to a recent observation in East Prussia: 'In spite of the fact that the drinking water showed an unusually high iodine content, there was a high percentage of goitre'

(Berlin correspondent, *J. Amer. Med. Assoc.*, 19th Nov. 1932, p. 1793). Orr and his colleagues have, in Great Britain, similarly failed to establish any correlation between goitre-incidence and the iodine content of drinking water; so also has Adlercruetz (1928) in Finland, and Keith (1926) and Walker (1932) in Canada; while Shore and Andrew (1929) appear to regard it as very doubtful in New Zealand.)

(6) It is possible that there is a critical value of iodine metabolism which controls the size of the thyroid gland. A low level, as represented by a low urinary excretion of iodine, is more likely to be associated with thyroid enlargement during the earlier stages of bodily development than after the physiological stresses of puberty are passed. There is a demand for a higher level of iodine in the thyroid gland at this period of life. It might well be argued that it is the physiological stress of puberty rather than want of iodine that determines thyroid enlargement at this period, though such want may contribute to it.

(7) The data provided by the estimation of urinary iodine in goitrous and non-goitrous persons, resident in a region of high endemicity of goitre (Gilgit, Himalaya), revealed no incontrovertible association between the occurrence of goitre and the amount of iodine excreted in the urine. It was thought possible that such association might have existed in females; but the possibility was remote. If it did exist, feminity determined it; there being no such association in males. Comparisons of this kind, when instituted between goitrous persons resident in one locality and non-goitrous persons resident in another, are not valid; to be so the comparison should be between persons of the same age, sex and social standing resident in the same locality.

(8) Certain surveys of iodine-level in the thyroid glands of normal and goitrous sheep and in some foodstuffs were examined; and the lack of incontrovertible association between the occurrence of goitre and a low level of iodine—in food and in the gland itself—was again revealed.

(9) The effect of adding iodine to a well-constituted diet may be anything from certainly harmful to definitely beneficial: harmful in causing the thyroid size to increase; beneficial in causing the thyroid size to decrease (see also Schmidtmann, 1932). It would seem that iodine serves to counteract the effect of disturbing influences—excess of lime, or of fats, or of certain goitrogenic substances of an unknown nature (*vide infra*)—in the diet, and thus manifests its beneficial action. An amount of iodine which may be sufficient when the diet is of one composition may not be sufficient when it is of another.

(The beneficial effect of iodine, in physiological doses, may be related to the improvement in nutrition which it brings about, and thus indirectly affect the thyroid gland. Hunziker (1920) and Hunziker and

Eggenberger (1924) have noted an increase both in height and weight of Swiss children receiving iodine prophylaxis, and greater weight of infants whose mothers were treated during pregnancy with iodized salt.)

(10) The general effect of adding iodine to diets deficient in vitamin-A-bearing substances was inconclusive; sometimes a reduction, sometimes an increase, in size of the gland was produced. In these dietetic circumstances iodine expressed its serviceability most markedly in the presence of insanitary condition. Insanitary condition contributed more than the non-administration of iodine, and deficient diet more than either, to producing and maintaining thyroid enlargement. Both the administration of iodine and the best possible sanitary condition may fail to prevent the occurrence of goitre in rats fed on diets deficient in vitamin-A-bearing substances; in these circumstances the administration of iodine may favour the occurrence of goitre.

(11) While iodine is a powerful anti-goitrogenic agent it was, in the aggregate, not found to be more so, in regard to the goitre-producing substance found in cabbage, than thymol, manganese chloride and thyroxine; all of which are antagonistic to the goitrogenic action of this substance. But iodine was more uniform in its anti-goitrogenic action than any of them.

(12) The anti-goitrogenic action of iodine has its limitations. It will not, for example, prevent the goitres which may arise in rats fed on certain diets deficient in vitamin-bearing food materials ('lymphadenoid goitre', 'ground-nut goitre', 'soya-bean goitre'); nor does a high content of iodine in the gland prevent the occurrence of 'scurvy goitre' in guinea-pigs. It will not prevent the compensatory hypertrophy following partial thyroidectomy in guinea-pigs (Leo Loeb, 1929); nor the colloid goitre which results from the ligation of the pancreatic duct in dogs (Sweet and Ellis, 1915; Davis *et al.*, 1932). On the other hand, its administration to animals may, as mentioned above, actually favour the occurrence of goitre or do harm in those suffering from it—as in rabbits suffering from 'cabbage goitre' (*vide infra*).

(13) There is no incontrovertible evidence that iodine deficiency is, *by itself*, the cause of goitre. The recent work of Hellwig (1931) and Jackson (1932) may be referred to in this connection. These observers failed to find that diets low in iodine were capable of causing goitre under experimental conditions in rats. The records of some such experiments, to be found in the literature, obviously relate to the effect of iodine administration to animals fed on ill-balanced diets rather than to the effect of iodine deficiency *per se*. Nevertheless, a low intake of iodine may, in certain circumstances of diet and hygiene, be a potent factor pre-

disposing to the occurrence of goitre, and may even be a determining cause of its endemicity.

(14) Iodine prophylaxis, though usually beneficial when physiological doses are employed, may, in certain circumstances, actually favour the occurrence of goitre. Particularly is this so when the diet is ill balanced, deficient in suitable protein and in vitamin-bearing ingredients. In this connection, compare the observations of Kirsch (1928) in malnourished school children (see also Schmidtmann, 1932).

My own view is that iodine insufficiency—an insufficiency brought about by a number of factors—is favourable to the occurrence of a certain type or types of goitre, but that it is not the essential cause of any type.

IX. CABBAGE GOITRE

The fortunate occurrence of endemic goitre in a colony of rabbits maintained by Chesney, Clawson and Webster (1928), in connection with their work on syphilis, has opened up a new page in the history of goitre research. Their colony was fed on a diet composed largely of cabbage (*Brassica oleracea*), and the cause of the goitre was ultimately traced by Webster and Chesney (1928) to this vegetable. The goitrogenic action of cabbage was confirmed by Marine and his co-workers in 1929 and by myself in 1930–1. (The results of one of my experiments were as follows: The weight of the thyroid per kilogram of body-weight was $5{\cdot}87 \pm 0{\cdot}66$ in well-fed controls and $25{\cdot}22 \pm 2{\cdot}16$ in rabbits fed exclusively on cabbage. Difference$=19{\cdot}36 \pm 2{\cdot}26$; $t=8{\cdot}6$; excess in cabbage-fed animals is, therefore, significant.) An exclusive diet of cabbage may cause goitre in rabbits within two months, and prolonged feeding upon it may result in large goitres in certain individuals. Individual idiosyncrasy is an important factor in its occurrence; some animals fail entirely to acquire it. The range of variability in size of the gland in cabbage-fed rabbits is very wide; in my own series the coefficient of variability was as low as 11·4 in one experiment and as high as 66·9 in another. Young animals are more susceptible than adults. Sex differences are trivial. In a series containing rabbits of a sufficiently wide range of age I found that the life-line of the gland in the goitrous group was of like shape and course to that in the control, non-goitrous group but located at a higher level; suggesting that the enlargement was mainly physiological in its nature. The time factor is important; for the longer the animals are fed on the diet the larger are the resultant goitres likely to be, provided always that the goitrogenic potency of the cabbage remains uniformly high. This potency varies greatly: it is profoundly influenced by season;

being greater in winter than in summer (Webster and Chesney, 1928; McCarrison, 1931; Webster *et al.*, 1931). Webster (1932) has provided some experimental evidence which at first sight would appear to suggest that it may be related to the intensity and length of exposure of the cabbage to sunlight. He found that artificially irradiated cabbage leaves had double the potency of non-irradiated leaves. This observation seems to conflict with the non-goitrogenic potency of summer cabbage (Coonoor); but it falls into line with the action of radiostoleum (*vide infra*) since irradiation, presumably, increases the vitamin-D content of the vegetable. A point of some interest in this connection is that the calcium content of the outermost leaves of cabbage may, in summer, be from twenty to thirty times as great as that of the inner leaves (Cowell, 1932). Patnaik, working in my laboratory, has recently found that the outer leaves of cabbage, maturing in February, contained as much as 78·0 μg. of iodine per kg., while the inner leaves ('heart') contained only 9·5 μg. In Coonoor the goitrogenic potency of cabbage appears to be related in some way to rainfall; being low or nil during periods of no or scanty rainfall and high during and after periods of heavy rainfall. The curve of potency, as determined by experiments in rabbits, follows closely upon that of rainfall in this locality. Goitres produced during the rainy season diminish in size during the dry season though the animals continue to be fed solely on cabbage. The goitrogenic potency of cabbage varies in different localities, and in the same locality it may vary from year to year. According to Marine and his co-workers (1930) cabbage is rendered non-goitrogenic by drying. He finds, also, that the expressed juice of the vegetable does not contain the goitre-producing substance while its tissues do. The potency of the cabbage cake, from which the juice has been expressed, is increased by washing in water; from which Marine concludes that the expressed juice contains one or more anti-goitrogenic substances. The goitrogenic agent is said to be insoluble in water, to be extracted by ether and other etherial solvents (Baumann *et al.*, 1931), to be heat-stable and to be resistant to oxidation in the air (Marine, 1930). In some of my own experiments steaming has enhanced its action, in others it has not; in the former its potency was already high, in the latter it was low. Acidity to the extent of pH 3·0 is said to increase the goitrogenic activity, and alkalinity to the extent of pH 9·0 to diminish it (Webster and Cipra, 1930).

The goitres produced in this way are of the hyperplastic type; they may contain little or no colloid. Cultural methods of study, such as those advocated by Houda (1928) have, in my hands, failed to reveal the presence of micro-organisms in them. They are associated with a lowering of the metabolism (Webster and Chesney, 1928, 1929); there is, apparently, an inverse relation between the size of the gland and the metabolic rate. The administration of iodine to the goitrous animals 'caused a marked increase in metabolic rate, rapid emaciation and, in most instances, death' (Webster and Chesney, 1928). The severity of this reaction bears a direct relation to the extent of the hyperplasia and, within certain limits, to the quantity of iodine administered. According to Baumann *et al.* (1931), a retention of calcium, magnesium and phosphorus occurs in rabbits fed exclusively on cabbage; it is prevented by the subcutaneous injection of potassium iodide. In my own series calcium retention did not occur until the thyroid had increased its size nearly threefold.

The iodine content of 'cabbage goitre' is in inverse relation to its size; and the urinary excretion of iodine by the goitrous animals is in inverse relation to the size of their goitres. The pH of the hyperplastic gland is significantly increased; so also is that of the testes. The H-ion activity of the blood is not altered nor is that of any other organ of the body; not, that is to say, to an extent which can be considered significant. There is no significant change in the size of other organs; the action of the goitrogenic substance is, in this respect, a specific one on the thyroid gland.

Certain food materials, such as bran, when added to an exclusive diet of cabbage enhance its goitrogenic potency; others, such as carrots, sprouted legume and fresh green grass, diminish it. Certain chemical substances—sodium chloride and radiostoleum—likewise enhance it; some—iodine, thyroxine, manganese chloride and thymol—diminish or wholly counteract it; while others, such as chlorine, are neutral. The addition of 1·5 mg. of iodine to the litre of drinking water prevents the occurrence of 'cabbage goitre'; so also does the bi weekly administration *per os* of 0·26 mg. of thyroxine to each rabbit; in neither case, however, may the gland contain colloid material though it be within or below normal limits of size. The preventive dose of manganese chloride was found to be in the neighbourhood of 2 mg. daily per rabbit; and of thymol 6 grains daily. The anti-goitrogenic action of thyroxine was more marked in degree but less uniform than that of iodine; no doubt because of its partial destruction in the alimentary tract. That of manganese chloride was equal in uniformity to that of thyroxine and in degree to that of thymol. The action of thymol was not uniform; for although in the aggregate it was as great as that of manganese, the drug did not prevent the occurrence of goitre in all the animals to which it was administered. Nevertheless, its anti-goitrogenic action was statistically demonstrated; thus confirming an observation made by me in 1906.

The goitre-producing properties of cabbage are not due to a deficiency of iodine in the vegetable. It has been suggested by Marine that they are due to some nutritional factor acting through the oxidation-reduction systems of the body. Cyanogen compounds are suspected in this connection; and, recently (1932) these observers have produced hyperplastic goitre in animals by the subcutaneous administration of cyanide; an observation which I have confirmed:

Two groups of six rabbits, previously fed on an exclusive diet of cabbage, were kept on the stock diet in use in this laboratory. One group acted as 'controls'; the other was given methyl cyanide, administered subcutaneously, for a period of twenty-one days.

The initial dose was 0·1 c.c. per rabbit daily; this being gradually increased up to 0·3 c.c. The mean 'r'-value of the thyroid gland, on the conclusion of the experiment, was 14·9 mg. in controls and 26·2 mg. in the group that received cyanide: an increase in size of the gland in the latter of 75 per cent. The effect of the cyanide was much more marked in some animals than in others. A repeat experiment yielded similar results: with cyanide, 22·7 mg.; without cyanide, 14·5 mg.

All cyanides, so far tested by Marine and his colleagues, caused thyroid hyperplasia in rabbits; some in greater and some in lesser degree. Methyl cyanide (acetonitrile: CH_3CN) produces the greatest reaction; the aromatic nitriles the least. But the amount of cyanide injected was considerable and, according to observations made in my laboratory (*vide infra*), greatly exceeded that derivable from the quantities of cabbage normally eaten by rabbits. Nevertheless, the merest traces of cyanide are known to be capable of causing profound depression of cell oxidation (Warburg), while the anoxemia produced by it (HCN) is known to cause thyroid hyper-function (Mansfield and Müller, 1912). The presence of cyanogen in cabbage is accordingly suggestive.

The hyperplastic goitre produced in rabbits by cyanide administration is preventable by the simultaneous administration of iodine (Spence and Marine, 1932). Some young rabbits are resistant to goitre produced in this way and fail to acquire it. The thyroid reactions obtained in rats and mice by this means are far less than those produced in rabbits receiving relatively much smaller doses (Spence and Marine, 1932). In my own experience the subcutaneous administration of sub-lethal doses of methyl cyanide to well-fed rats, for a period of thirty-five days, caused no enlargement of the gland: its mean size ('r') being 10·0 mg. as compared with 9·9 mg. in controls. On the other hand, its administration to rats fed on a synthetic diet deficient in vitamin A (to which no iodine was added) caused the gland to be larger than in controls (10·7 mg. as compared with 8·2 mg.) though not significantly larger than in well-fed rats to which cyanide was not administered.

(An investigation into the nature of the goitrogenic agent in cabbage, carried out in my laboratory, has yielded the following results: On autolysis, cabbage of high goitrogenic potency gave a faint reaction for cyanides. On emulsion hydrolysis it yielded fair amounts of sulphocyanides and hydrogen sulphide, and traces of cyanides; the amount of cyanides being of the order of 0·8 mg. per kg. Alpha-hydroxy-carboxylic acids and aromatica mines (primary and tertiary but not secondary) were also present. Cabbage fermented with the enzymes from the gastro-intestinal tract of rats yielded more sulphocyanides than when fermented with the enzymes of the gastro-intestinal tract of rabbits. The presence of cyanogen and sulphocyanide following enzyme hydrolysis of cabbage indicates the existence in it of a precursor of these substances, probably a cyanogenetic glucoside. Marine and his colleagues (1932) did not definitely isolate cyanide in cabbage. Ranganathan (1933), working in my laboratory, finds that fresh cabbage in this locality (Coonoor) contains on tartaric acid distillation 3·45 mg. of CN, and 6·26 mg. on sulphuric acid distillation, per kg.)

While the evidence so far available tends to connect cyanide with the causation of 'cabbage goitre' it cannot at present be definitely stated that it is the essential or direct cause, though it is possible that it may be ancillary to that cause. Nevertheless, several important facts have emerged from these studies: the existence in certain food materials of *positive* goitrogenic factors—as opposed to the *negative* one of iodine deficiency—has been demonstrated; while it has been shown that substances which depress cell oxidation may increase thyroid activity and that cyanides are to be included in this category.

Saponins or, more properly, sapotoxins—glucosides occurring in cabbage and widely distributed throughout the vegetable kingdom—are also suspect in this connection (Stiner, 1933). This suggestion has attractions, but, so far as I am aware, no experimental evidence has yet been advanced in support of it.

X. GOITROGENIC AND ANTI-GOITROGENIC FOOD MATERIALS

Marine and his collaborators (1930) have incriminated other members of the *Brassica* family and some *Cruciferae* as goitrogenic food materials. Some of the former are more potent than others; a fact also observed by Stiner (1933). In my own laboratory we have found that soya bean and ground-nut (both poor in vitamin A) gave rise to goitre when they formed 10 to 15 per cent of synthetic diets, deficient in vitamins A and C but containing iodine in the form of potassium iodide. Sorghum

(*Andropogon*) also was found to increase the size of the thyroid gland in rats when it formed 20 per cent of an otherwise neutral diet—neutral, that is to say, in the sense of being neither goitrogenic nor anti-goitrogenic. These food materials yield, on enzyme hydrolysis, approximately the same amount of cyanide as winter cabbage, but I have not observed that so low a concentration of cabbage in the diet as 10 to 20 per cent is capable of causing goitre—either in rabbits or in rats. Having regard to the histological features of the goitres produced in rats by means of soya bean and ground-nut—which reveal unmistakable evidence of the effect on the gland of vitamin-A-deficiency—I, at present, attach more significance to the known action of this deficiency in favouring goitre production than to the assumed goitre-producing action of the cyanide content of the soya bean and ground-nut. It is possible, however, that vitamin deficiency may favour the action of the cyanide or other noxa contained in these foods; recent observations of Stiner (1933) point in this direction. In this connection it is of interest to note that deficiency of vitamins A and B diminishes the resistance of mice to intoxication by acetonitrile (Blanchard *et al.*, 1931).

It is significant that rats fed on the vitamin-deficient diets, containing ground-nut or soya bean, develop goitre despite the ingestion of relatively large amounts of iodine in the form of potassium iodide. The 'r'-values of the thyroid in these experiments were as follows: controls, 6·63 mg.; ground-nut, 21·69 mg.; soya bean, 17·2 mg.

The food materials so far found to possess goitrogenic properties do not cause goitre unless they form a relatively high proportion of the diet or, as in the case of soya bean and ground-nut, unless the diet is deficient in vitamin-bearing constituents; they are, therefore, neutralized by others that are 'anti-goitrogenic' in their nature. Certain vitamins, whole milk, carrots, oatmeal, fresh green grass and sprouted legumes come into the latter category; with them are to be included others—fresh alfalfa, skunk cabbage and the expressed juice of steamed cabbage—mentioned by Marine *et al.* (1933). The anti-goitrogenic properties of these substances appear to be independent of their iodine content; thus, oatmeal, which has a low iodine content, is definitely anti-goitrogenic when added to a cabbage diet; it also confers on mice (Reid Hunt, 1910) a high degree of resistance to methyl cyanide.

Some food materials when subjected to enzyme hydrolysis yield traces of cyanides; others yield traces of the less toxic sulphocyanides. Ranganathan (1933), working under my direction, has examined some forty food materials from this point of view. He has found that those yielding cyanides (cabbage, sorghum, soya bean, ground-nut and linseed meal) are amongst the food materials shown in my laboratory to possess goitrogenic properties; while those yielding sulphocyanides (milk, oatmeal, green grass, sprouted gram and carrots) are amongst those shown to be neutral or to possess anti-goitrogenic properties. Evidence has also emerged which would appear to indicate that cyanogenesis is related to H-ion concentration in the gastro-intestinal tract; an observation which, if confirmed, will bring the state of the tract and the nature of its bacterial flora into the aetiological picture. This work is still in progress.

It has recently been stated by Marine and his co-workers (1933) that the anti-goitrogenic agent present in certain food materials is probably hexuronic (ascorbic) acid. They report that the administration of sufficient amounts of this acid prevents both 'cabbage goitre' and 'cyanide goitre'. In this connection attention may be drawn to the facts that ascorbic acid is apparently identical with vitamin C; that goitre is not invariably, nor even frequently, associated with scorbutic states either under natural or experimental conditions; and, that while cabbage is relatively rich in ascorbic acid and carrots, for example, relatively poor in it (Birch, Harris and Ray, 1933) the former vegetable is definitely goitrogenic while the latter is definitely anti-goitrogenic.

It is apparent from these considerations that food materials are of two kinds—'goitrogenic' and 'anti-goitrogenic'—and that the normal size of the thyroid gland is largely dependent on their right admixture in the diet. Further, some food materials which are goitrogenic in one set of circumstances may be anti-goitrogenic in another. Examples of this kind have already been cited. Because certain food materials are thus classed as 'goitrogenic' it is not to be supposed that they are, therefore, to be avoided. On the contrary, they may be—and, indeed, the known goitrogenic food materials are—of high nutritive value. It is a question rather of their relation to other constituents of the diet. The truth which I enunciated earlier in this Report is thus brought again into prominence: the more perfect the constitution and balance of the diet, the more normal will be the size, and the more normal the action, of the thyroid gland. The work of Reid Hunt, in 1910, and of Abelin, within recent years, on the relation of nutrition to thyroid activity, points in the same direction.

XI. INTERACTION BETWEEN DIET AND INSANITARY CONDITION IN THE CAUSATION OF GOITRE

It was pointed out above that the goitrogenic potency of cabbage is slight or nil during the dry months of the year in Coonoor. Advantage was taken of this fact to devise a 'neutral' diet (neither goitrogenic nor anti-goitrogenic) suitable for rats. An exclusive diet of cabbage was found to be highly toxic for young (30- to 40-day-old) rats; causing the death of a high proportion of them in forty-eight hours and of all of them within four days. The diet ultimately evolved consisted of 60 parts of fresh raw cabbage, 20 parts of sorghum (*Andropogon*), 20 parts of whole-wheat flour and distilled water. The iodine content of this diet was 15·28 μg. per kg.

Two groups of young albino rats, from the same non-goitrous stock, were fed on this diet for a period of 110 days during the dry months of the year (1931). These groups—the one consisting of 129 animals, the other of 133—were as similar to one another with respect to initial body-weight, age and sex distribution, etc., as it was possible to make them. The one group—referred to as 'sanitary'—lived under conditions of perfect sanitation; the other—referred to as 'insanitary'—lived under conditions of gross insanitation. These conditions are described elsewhere (McCarrison and Madhava, 1932); but here it may be said that yeast played a conspicuous part in the fermentation processes occurring in association with them.

At the end of the experiment the animals were killed and the thyroid glands removed and weighed with the usual precautions against loss of weight by drying. It was found that there was no significant difference in the final body-weights of the two groups; a circumstance which rendered their comparison easier. The results of the experiment were as follows:

(i) The mean thyroid-weight in the 'sanitary' group was 8·30±0·14 as compared with 22·27±0·73 in the 'insanitary' group.

(ii) The mean thyroid-size ('r') in the 'sanitary' group was 6·69±0·12 as compared with 15·74±0·32 in the 'insanitary' group.

The incidence of 'true goitre', as determined by the criterion, mean 'r'$+2{\cdot}5\delta$, was 46·6 per cent in the 'insanitary' group; the 'sanitary' group was goitre-free. Its incidence was higher in females than in males. The addition of dried yeast, in the proportion of 1 gramme per rat per day, to the neutral diet increased significantly the size of the goitres produced by insanitary condition. Thymol in doses of 1 grain per rat daily did not prevent them.

(iii) The frequency distribution both of thyroid-weights and of thyroid-sizes ('r') exhibited 'positive skewness' in marked degree: those of controls yielded a normal, or nearly normal, probability curve. It was found, moreover, that while the 'r'-curve (life-line) of the gland in the controls was of normal shape and course, that of rats living in insanitary condition rose continuously and departed more and more from the normal course.

The goitrogenic agent, associated with the insanitary conditions prevailing in this experiment, not only caused thyroid enlargement but caused the enlargement to increase with increasing body-weight and age; a result in sharp contrast to that exhibited by the life-line of the gland in 'cabbage goitre', which follows the normal course more closely though at a higher level.

These results are significant. They indicate that the neutral diet was not of itself goitre-producing; indeed, the size of the gland in the control group ('sanitary') was less than that in standardized stock animals, and approximately the same as in rats fed on a well-balanced vegetarian diet. They indicate, further, that in the presence of this diet the conditions of insanitation to which the animals were subjected had a pronounced goitrogenic action.

The effects of these conditions of insanitation on other organs of the body were of great interest. They were exhibited as a significant (statistically speaking) increase in size ('r') of the adrenal glands and spleen, an increase in size, though not in weight, of the liver, and a diminution in size of the testes and thymus. The heart and kidneys remained unaffected in point of size. The pituitary was not examined. The goitre itself had no correlated effect on the heart nor on other organs of the body.

In a further experiment four similar groups of young rats were fed, during the same dry season and throughout the period of the summer rains (1932), as follows: Two groups on the neutral diet and two on the stock diet in use in this laboratory, but augmented with a more liberal supply of whole milk (an augmentation which, as has been shown above, completely excludes goitre in hygienically caged, stock rats in Coonoor). Of the two groups fed on the neutral diet one lived under conditions of perfect sanitation, the other under conditions of gross insanitation. Similarly, with those fed on the 'anti-goitrogenic' diet. The results of the experiment were as shown in the table on p. 69.

These results are again significant. They indicate that neither diet was in itself goitre-producing; that bad sanitary condition had a marked goitrogenic action in the presence of the neutral diet; and, that the stock diet, with additional milk, counteracted the goitre-producing influence of insanitation. Further, an analysis of the individual 'r'-values in Group 2 showed that, with increasing body-weight, these were maintained at a high level.

The existence of a goitrogenic agent in association with the conditions of insanitation prevailing in these experiments is thus demonstrated; and the importance of food in favouring or disfavouring its action, is likewise proven.

	Weight of the Thyroid in mg. per 100 gm. of Body-weight 'r'	*Incidence of True Goitre (%); Glands Exceeding Mean ('r')+2·5δ, or 15 mg.*
1. Neutral diet: good sanitary condition	8·1	0·0
2. Neutral diet: bad sanitary condition	16·7	56·2
3. Anti-goitrogenic diet: bad sanitary condition	8·6	0·0
4. Anti-goitrogenic diet: good sanitary condition	8·2	0·0

XII. GOITRE NOXA

The conditions of insanitation referred to in the preceding experiments led to the accumulation in the insanitary cages of a compost of fermenting excreta and food remnants. While the fermentation process was at its highest, and rats were still inhabiting these cages, this compost was extracted with distilled water: 200 gm. to the litre. The mixture was allowed to stand in stoppered bottles for forty-eight hours or more. Thereafter it was filtered: one part through microbe-proof porcelain candles (Cheavin's) under pressure; the other through several layers of muslin. The first may be referred to, for convenience sake, as 'sterile filtrate', though its sterility was not long maintained; the second as 'unsterile filtrate'. Four groups of young rats—thirty-six in each—selected with the same care as in the previous experiments, were confined in separate, screened cages under conditions of meticulous cleanliness and fed on the 'anti-goitrogenic' diet referred to above. The sole source of drinking water of three of these groups was one or other of the above filtrates; and to ensure that the animals ingested a sufficient quantity of them, the filtrates were intimately mixed with the food. They were provided in the proportion of 10 c.c. per rat daily: an amount equivalent to 2 gm. of the compost. One of the groups received the sterile filtrate alone; a second the sterile filtrate to which iodine, in the proportion of 10,000 to the litre, was added. A third group received the unsterile filtrate; and the fourth (controls) an equivalent amount of distilled water. The experiment was continued for a period of 181 days. At the end of this time the animals were weighed, killed, and their thyroids removed in the usual way. The results were as follows:

Rats Receiving:	*Mean Weight of Thyroid, in mg. per 100 gm. of Body-weight ('r')*
1. Sterile filtrate	6·7
2. Sterile filtrate plus iodine	7·7
3. Unsterile filtrate	9·2
4. No filtrate (controls)	8·8

It is obvious from these figures that the size of the thyroid gland did not exceed normal limits in any of the four groups. An examination of the frequency distribution of the thyroid-weights and thyroid-sizes did not reveal the existence of goitre; nor was its existence revealed in any case by the criterion, mean 'r'$+2{\cdot}5\delta$. On the contrary, there was a definite tendency to the prevalence of unusually small thyroid-sizes in the groups receiving sterile filtrate; an observation recalling the results observed many years ago (McCarrison, 1909) in well-fed goats receiving cultures of faecal bacteria and their products.

Histological examination of these glands revealed results of great interest:

Six sample glands were taken at random from each of the four groups. They were fixed with as little delay as possible and serially sectioned. Those from the control group were of normal histology; those from the other three groups exhibited degenerative changes in approximately 50 per cent of cases. These degenerative changes were of an order similar to these seen in certain systematic infections and severe toxaemias: desquamation of epithelium, breaking down of the follicular walls, death of many acinous cells, disappearance of colloid, and hyaline degeneration. In some specimens many small, rounded, densely-staining nuclei were found to be more or less uniformly distributed in a hyaline matrix or arranged in irregular clumps or heaped-up masses. Occasionally, the appearances resembled those of the parenchymatous or diffuse type of adenoma in the human subject; many, small, closely-packed follicles, mainly devoid of colloid. These changes were occasionally confined to one lobe or one lobe was more affected by them than the other. Sometimes they were limited to the more central part of the lobe; sometimes the whole, or the greater part, of the lobe was affected by them.

These results recall those of Alexandresco and Lautier (1931), following the buccal administration to monkeys of organisms associated with rheumatism: diplo-streptobacillus. Repeated and prolonged administration of the *forme diplococcique* resulted, after six weeks, in an intense degeneration of the parenchyma of the thyroid gland; while, after three months' administration, the *forme bacillaire* gave rise to a diminution in size of the gland with fibrous and adenomatous changes.

A further experiment was undertaken in which a watery extract of the drying compost from the uninhabited, insanitary cages was used. Four groups of rats were caged under conditions of meticulous cleanliness and fed as follows: Two on the stock diet with additional milk and two on the cabbage-sorghum-wheat diet referred to above as neutral. But the experiment was carried out during the winter months (1932–33), at a time, that is to say, when the goitrogenic potency of cabbage is at its highest in Coonoor. The neutral diet was, therefore, no longer 'neutral' but definitely goitrogenic.

(Attention may here be drawn to the varying goitrogenic potency of this diet, consequent on seasonal conditions or on the quality of its ingredients in different years or seasons. Hygienically-caged rats, fed upon it during the spring, summer, autumn and early winter of 1931, had thyroid glands whose mean size ('r') was 10·38 mg.; the percentage incidence of true goitre being 7. Those fed upon it during the dry season of 1932 had thyroids whose mean size was 6·69 mg.; the percentage incidence of true goitre being nil. Those fed upon it during the same dry season and into the period of the summer rains had thyroids whose mean size was 8·1 mg.; the percentage incidence of true goitre again being nil. Those fed upon it during the winter and early spring months of 1932–3 had thyroids whose mean size was 14·4 mg.; the percentage incidence of true goitre being 38·9.)

One group fed on the well-constituted diet and another fed on the cabbage-sorghum-wheat diet received the watery extract of the compost as their sole source of drinking water; the other two (controls) were given distilled water. The results of the experiment were as shown in the table on p. 72

It is apparent from these results that the cabbage-sorghum-wheat diet was, on this occasion, definitely goitrogenic and that the watery extract of the compost had a marked goitre-producing action. This action was manifested only to a slight extent in rats fed on the well-constituted diet, but in those fed on the cabbage-sorghum-wheat diet it was—as evidenced by the higher mean size ('r') of the gland and the high incidence of goitre—pronounced.

An analysis of the individual 'r'-values revealed that while they declined steeply with increasing body-weight in Group III, the decline was much less steep in Group IV. The difference in height of the

Group	*Diet*	*Mean Size ('r') of the Thyroid, mg. per 100 gm. of Body-weight*	*Percentage Incidence of True Goitre; Glands in Excess of Mean 'r'+2·5δ*
I.	Well-constituted diet; distilled water	10·9	nil
II.	Well-constituted diet; watery extract of compost	11·5	8·3
III.	Cabbage-sorghum-wheat diet; distilled water	14·4	38·9
IV.	Cabbage-sorghum-wheat diet; watery extract of compost	17·8	88·9

'r'-curves in these two groups is the measure of the goitrogenic action o
the watery extract of the compost.

This experiment affords conclusive proof that the goitrogenic agent
associated with certain conditions of insanitation can be water-borne
and that its action is to a great extent disfavoured by a perfectly constituted diet and favoured by an ill-constituted one. It can hardly be
doubted that this agent is a living organism or the product of such a
organism.

(It may here be mentioned that the watery extract of the compos
yielded traces of cyanides on enzyme hydrolysis. It contained tyramine
in relatively high concentration. It had a pronounced effect on thyroi
tissue grown *in vitro*. When added to the culture medium in the proportion of 1 part to 5,000 parts of the medium it caused complete inhibitio
of growth and rapid disintegration of cells that had already grown
When its concentration was reduced to 1 part in 50,000 parts of the
medium it stimulated growth. The part played by tyramine—the product of certain strains of the colon bacillus—in the production of goitre
has recently been emphasized by Davis *et al.*, 1932.)

In this connection attention may be drawn to the Report on The
Aetiology and Epidemiology of Goitre which I had the honour t
present to this Conference in 1927. Therein I recorded the results of my
earlier experimental work and indicated the part which intestinal an
other bacteria may play in the causation of goitre in adult animals an
of congenital goitre and cretinism in their offspring.

Attention may also be directed to the recent observations of Turcu
(1931). He found that certain strains of colon bacillus, isolated fro

cases of endemic goitre and grown for two years, were agglutinated in 62 per cent of cases by the sera of goitrous persons; no agglutination occurring with the sera of non-goitrous persons.

The work of Womack, Cole and Heidmann (1928, 1929, 1931) is also of great interest in this connection. They have confirmed and extended the observations of earlier workers (Rogers, Garnier, Torri, Crispini, Sejous, de Quervain, Farrant and others) in regard to the effects on the thyroid gland of certain infections and severe toxaemias. They find that the first effect of chemical and microbic substances is to increase the functional activity of the gland; that continued stimulation by these substances leads to hyperplastic changes; and that adenomatous and fibrotic changes result if the stimulation be intense. Organisms inhabiting the intestinal tract appear to be more prone to produce these changes than the pyogenic group. In this connection see also the results of Rush and Jones (1924) on the experimental production of goitre in rabbits by means of faecal extracts.

A recent observation of Anderson (1933) may also be referred to here. She finds that while subcutaneous injection of an alkaline extract of the anterior pituitary lobe does not cause thyroid enlargement in rats, the simultaneous injection of the toxins of staphylococcus (intraperitoneally) gives rise to marked hyperplasia and enlargement of the gland with symptoms simulating those of Graves' Disease.

Twort and Twort (1932) have reported some interesting observations in regard to the effects on the thyroid gland of the continued application of carcinogenic petroleum and shale oils or tars to the skin of mice. Thyroid enlargement was produced by this means in a high proportion of mice; it was not prevented by the enrichment of the diet. Even in glands that were not enlarged pathological changes were often found on microscopical examination.

('The commoner features of the enlarged thyroid glands were: inflammation, usually chronic, but sometimes acute, with haemorrhages and congestion; hyaline degeneration, especially of the stroma; hypertrophy and hyperplasia; diffuse adenomatous condition; cystic formation (colloid goitre); true adenoma; carcinoma. Several of these features were frequently found in the same gland. The diffuse adenomatous or papillomatous condition was very commonly met with, especially among the older animals. Such glands may be congested with some lymphocytic infiltration, often focal, or more usually they are anaemic with conspicuous colloid deficiency. About 25 per cent of the diffusely adenomatous glands were cystic in nature, and were largely composed of dilated vesicles filled with colloid' (Twort and Twort, 1932).)

It is apparent, therefore, that a variety of toxic substances, both chemical and microbic, are capable of giving rise to goitrous changes in the thyroid gland.

XIII. SUMMARY OF CAUSES OF GOITRE

Apart from such influences as hereditary predisposition, individual idiosyncrasy, puberty and pregnancy, the facts dealt with in this Report seem to me to show that there are four 'evident and conjunct' causes of goitre:

(1) Increased demand on the part of the body for the products of the thyroid gland; such as may be occasioned by an excess of certain substances (fats, lime and the goitrogenic agent in some vegetables) in the food.

(2) Faulty nutrition of the gland, with depreciation in functional efficiency of the glandular epithelium and increased susceptibility to the action of toxic and microbic agencies; such as may be occasioned by deficiency of suitable protein and of certain vitamins in the diet.

(3) The action of toxic substances on the gland; such as that of some chemical poisons, of the toxins of certain intestinal and other bacteria, and of the goitrogenic agent associated with insanitary condition.

(4) Lack, or insufficiency, of certain food essentials; such as of some vitamins, hexuronic (or ascorbic) acid, iodine, phosphates and certain unidentified anti-goitrogenic substances in food.

It is apparent that these causes of goitre may interact with one another in various ways, and that in some circumstances one cause may be dominant, in others another.

XIV. CONCLUSIONS

This, Gentlemen, is the account I have to give of the progress made in regard to knowledge of the causation of goitre since the date of the last conference. It is a considerable progress; more rapid, perhaps, than at any previous stage of goitre research. It is evident from it that the causes of goitre are multiple and their effects manifold; that some of these causes are now definitely known to us; that they are mainly nutritional and hygienic; and that their combination in various ways may give rise in different persons and in different localities to different types of goitre both of a sporadic and of an endemic kind. True endemic goitre, with its sequelae of congenital goitre and cretinism, is due, I believe, to a summation of these causes; and, as I said at the last conference—but to-day with more assurance—we have now the means of preventing it 'by attention to the fundamental principles of nutrition and of personal and social hygiene'. I venture to think that the stage of 'theory' in regard to the aetiology of endemic goitre is passed. We are now in the region of proven facts. The time has, therefore, come to abandon all theory and all dogma and to proceed with the accumulation of fresh facts. In the accumulation of these facts it is essential to employ exact methods of numerical exploration such as those I have endeavoured to indicate to you; to adopt biometric means of scrutiny and control of our observations; to establish standards of normality both statistical and histological; and to use for experimental purposes only those animals that have been standardized by minute attention to breeding, hygiene and diet. Only in this way can we accumulate the precise data that are needed for the elucidation of the remoter mysteries which still surround the aetiology of the protean malady we call 'Goitre'.

CHAPTER III

Researches on Deficiency Disease, 1918–1935

In perusing[1] the literature of disease due to deficiency of certain accessory food factors, one cannot fail to be struck with the fact that there are some directions in which inquiry has been almost wholly neglected. The want of substances essential for the normal metabolism of the human or animal body suggests the need for examining the effects of their deficiency on the organs responsible for digestion and assimilation and for the regulation of metabolic processes. Yet our knowledge of these effects is very scanty. The influence of 'vitaminic' deficiency on the adrenal glands, on the pancreas, on the liver and the spleen is, so far as I can ascertain from the available literature, unknown; while that on the thyroid apparatus has been but incompletely studied. Nor are we better informed with respect to other important structures as, for example, the pituitary gland and the reproductive organs. It has seemed to me desirable, therefore, to attempt to fill some of these gaps in our knowledge.

The morbid anatomical findings which I have to record will, I hope, aid in a clearer comprehension of the genesis of diseases resulting from deficiency of certain accessory food factors; not only as regards their grosser evidences, as exemplified by beri-beri, but also as regards their minor manifestations. It is rare that the physician, outside the Tropics, meets with morbid states resulting from complete deprivation of accessory food factors. My own clinical experience leads me to believe that many are the minor maladies associated with the incomplete provision of these substances in the food of children especially, or with their incomplete assimilation.

In considering these problems in the laboratory it is necessary to observe the results of 'vitaminic' deficiency in healthy animals and also to consider them in connection with other pathogenic factors which may operate in nature. For example, both inanition and a diet too rich in starch and too poor in 'vitamines' lead to depression of pancreatic and gastro-intestinal function. If these organs are exposed in addition to the influence of toxic or bacterial agencies their depression will be manifestly greater. The purity of laboratory experimentation is rarely repeated in nature. The manifold toxic influences to which human beings are subjected, under conditions of food deficiency, must play an important part in further depressing the functional activity of those organs and tissues on which normal metabolism is dependent. The toxic products of intestinal bacteria, or intestinal parasites, may thus assume a role of considerable importance in the genesis of morbid states which are no doubt initiated by the dietetic defect. Many observers have attached considerable aetiological significance to ankylostomiasis in beri-beri; for my part I have no doubt that they were right. For if the human body requires a modicum of 'anti-neuritic vitamine' we may be certain that nematodes and cestodes need it no less. Thus if the food entering the digestive tract contains too little of these substances the presence of such parasites in the upper part of the small bowel may be the determining factor in the genesis of deficiency disease.

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[1] Extract from number 67 in Bibliography.

During the year 1914, and during the present year (1918), I fed a large number of pigeons on a diet consisting solely of polished rice: that is to say, on a diet composed mainly of starch, with less than 10 per cent of protein and with complete (?) absence of the so-called accessory food factors. One hundred and sixty-eight of these birds developed *polyneuritis columbarum* within the period of the experiments. The heart's blood and internal organs of 142 birds so fed were examined bacteriologically at autopsy: of these 94 were found (mostly in 1914) to have had concurrent septicaemic infections of various kinds, while the heart's blood and organs of 48 were sterile.

Seventy-two pigeons were used as controls: the blood and internal organs of 63 were examined bacteriologically at the time of death. Six were found to have septicaemic infections of various kinds.

It is clear, then, that other agencies, in addition to lack of accessory food factors, may contribute to the genesis of those morbid states which are initiated by dietetic deficiency. In surveying my laboratory records I find that four chief factors are concerned in the production of these morbid states. These are:

(1) Inanition.
(2) Excess of starch in the food.
(3) Lack of accessory food factors, and
(4) Pathogenic organisms.

The influence of the first three is constant, of the last fortuitous.

I propose now to present the evidence upon which this general conclusion is based. Before doing so, however, it is necessary to draw attention to the importance of demonstrating the sterility of the blood and tissues in all cases before accurate conclusions can be drawn as to the effects of the food deficiency factor alone. This is especially necessary when dealing with the endocrine glands. The thymus, the thyroid, the adrenals and the testicles are highly susceptible to the action of bacterial agencies. Consequently, without demonstrating their absence, conclusions with regard to these organs may be erroneous.

The present paper is confined mainly to a consideration of clinical and gross morbid anatomical findings. Certain histological observations, made for diagnostic purposes, are also recorded. It is hoped to supplement these, as opportunity affords, by more complete histo-pathological studies which will form the subject of future communications.

The paper is divided into three parts: the first dealing with the effects of inanition alone; the second with the effects of a milled and autoclaved rice dietary alone; the third with the effects of this dietary in association with septicaemic states.

I. THE EFFECTS OF INANITION

1. *Clinical Observations*

The effects of inanition were studied in six pigeons—two males and four females. These were confined in separate cages and deprived of all food. Water was introduced into the crop twice daily by means of a syringe. The birds survived for an average period of twelve days.

The average weight of the birds on the initiation of the experiment was 266 gm.; at its termination 206 gm. The loss of body-weight thus amounted to about 5 gm. daily.

Apart from progressive asthenia and adynamia, the most notable features presented by these birds, on clinical examination, were a progressive fall in body temperature and progressive slowing of the respirations. These observations were made in the forenoon of each day.

It will be shown that the changes in body temperature and respirations are common alike to birds subjected to inanition and to those fed on a diet consisting solely of milled rice, always provided that septicaemic states are absent.

2. *Anatomical Observations*

Apart from the generalized atrophy the most marked features in these birds were: (1) the enlargement of the adrenals; (2) the band of oedema replacing the band of fat at the auriculo-ventricular junction; and (3) the pronounced changes in the pancreas.

While the effects of starvation in producing generalized atrophy of the body tissues, fall of the respiratory quotient, acidosis, and even degenerative changes in tissues' cells—as, for example, in those of the liver and nervous system—are well known it has seemed to me essential to establish, by weighing the organs, a mathematical basis for comparison with conditions in which the food was qualitatively deficient. The number of birds employed is small but is sufficient for the purpose in view.

In the table on p. 94 the weights of these organs are contrasted, per kg. of body-weight, with those of controls and of birds fed solely on milled rice. The organs of birds dying of inanition fall into three categories when contrasted as regards weight with those of healthy birds:

(i) Those which undergo hypertrophy: the adrenals.

(ii) Those which undergo atrophy (the degree of atrophy being in the order named): the thymus, testicles, spleen, ovary, pancreas, heart, thyroid, liver, stomach, kidneys, pituitary and the intestines, which, however, were not weighed.

(iii) Those which remain unchanged: the brain.

The atrophy of the thymus, the reproductive organs, the spleen and the pancreas is proportionately greater than that of the body as a whole. That of the liver and the heart is more proportionate in this regard. It would seem that the more urgent needs of the adrenals, brain, pituitary, kidneys, thyroids and heart for proteins, fats, glycogen, 'vitamines', and salts are supplied at the expense of the thymus, the reproductive organs, the spleen, the pancreas and the liver.

These findings afford an interesting contrast to those presently to be recorded in birds fed on milled rice It will be observed that while the atrophy and hypertrophy are alike in kind, in birds of the two classes, they are greater in degree in birds subjected to inanition. In the one class inanition is acute in its progress, in the other it is more prolonged. These results, I think, leave little room for doubt but that inanition is an important factor in the genesis of those morbid states resulting from a sole diet of polished rice.

(i), (a) THE ADRENAL GLANDS IN INANITION

The most remarkable of these findings is the enlargement of the adrenals: it is one to which I can find no previous references in the literature of endocrinology.

This enlargement appears to be a true hypertrophy, since it is associated with a corresponding increase in the gland's content of the medullary secretion, adrenaline.

The adrenals of two pigeons, dying as a result of inanition, were removed immediately after death, weighed, and pounded up in a sterile mortar with 5 c.c. 0·85 per cent NaC1. In two other cases the birds were killed when at the point of death, and the glands similarly weighed and emulsified in saline. The emulsions were injected into the left jugular vein of two sheep under ether anaesthesia, kymographic tracings of the arterial blood-pressure being taken from the right carotid. The observations were controlled either by injecting into the same sheep the emulsified adrenal glands of healthy birds, or by the injection of 0·1 mg. of adrenaline, the commercial solution (one-in-thousand) being employed for the purpose. The results are tabulated on p. 81.

The kymographic results indicate that the adrenal hypertrophy of inanition is associated with a corresponding increase of adrenaline. It will be observed from this table that sheep vary greatly in their susceptibility to adrenaline introduced intravenously; 0·1 mg. causing a rise of blood-pressure of 34 mm. of Hg. in one and 82 mm. in another. This variation is largely dependent upon the initial blood-pressure of the animal at the time of observation. Metabolic idiosyncrasy, however, is mostly responsible for it. The depressor effect exercised by the adrenals of birds dying of in anition ismuch less marked, and the subsequent pressor effect much more marked than in the case of healthy adrenals or of adrenaline itself. This change is even more pronounced in cases of wet beri-beri.

3. *Conclusions*

(1) Pigeons deprived of all food, with the exception of water, die in an average period of twelve days.

(2) During this time they lose weight to an average extent of 23 per cent of their original body-weight.

(3) Certain organs undergo atrophy: the thymus, the testicles, the spleen, the ovary and the pancreas being most affected in this regard the atrophy is most marked in the order in which the organs are named

(4) As a result of inanition, the adrenal glands undergo hypertrophy with increase of their adrenaline content.

(5) A comparison of these findings with those observed to result from a sole diet of milled and autoclaved rice, indicates that inanition plays an important role in the genesis of the morbid states resulting from this dietary.

Effects on arterial blood-pressure of sheep of the intravenous injections of emulsified adrenals from healthy and starved pigeons

No. of Pigeon	*Healthy or Diseased*	*Weight of Adrenals in mg.*	*Weight of Sheep in lb.*	*Initial B.P. in mm. of Hg.*	*Primary Rise of B.P. in mm. of Hg.*	*Succeeding Fall of B.P. in mm. of Hg.*	*Final Rise of B.P. in mm. of Hg.*
158	Healthy	16	35 Same sheep	120	Nil	18	8
	0·1 mg. adrenaline	—	35	108	12	22	34
127	Inanition	28	35	110	22	14	46
116	Beri-beri[1] (Hydropericardium)	72	35	114	24	20	72
124	Inanition	28	33 Same sheep	74	35	2	100
111	Beri-beri[1] (Oedema)	53	33	86	38	Nil	124
123	Inanition	40	33	60	Nil	Nil	102
	0·1 mg. adrenaline	—	33	54	Nil	Nil	82
122	Inanition	31	33	54	Nil	Nil	68

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[1] The word beri-beri is here used as a synonym for *polyneuritis columbarum*

II. THE EFFECTS OF A DIET OF MILLED AND AUTOCLAVED RICE

The effects of a sole diet of milled and autoclaved rice were studied in thirty-four pigeons whose heart's blood and organs were demonstrated to have been sterile at the time of death and in which minute post-mortem examinations were made.

1. *Details of Experiments*

Previous to the commencement of the experiments the pigeons employed were living in a semi-wild state. They were adult birds, imported from Coimbatore and other parts of southern India, where beri-beri does not occur. An attempt was made to procure wild birds as previous experience had shown that, so far as the endocrine organs are concerned, domestication is sufficient in itself to alter materially their histological appearances. I was not successful in obtaining wild birds, but fortunate enough to obtain a large number which were semi-wild; that is to say, they were dependent for their food on the crops and had not been previously confined. I consider this precautionary measure with regard to the choice of animals to be of importance.

(i) The birds were confined in new cages as follows:

(a) Twelve pigeons in each of four netted-wire cages having the following dimensions: 5′×3′×2′. In two of these cages the floor, as well as the sides and top, was of netted wire, the object being to permit the grains falling from the feeding troughs, as well as the droppings of the birds, to fall through into a zinc bottom below, thus avoiding as far as possible faecal contamination of the food. The birds in one of these cages received a liberal diet of mixed grains including sand and a small daily allowance of *mung dal*; those in the other received milled rice only.

The remaining two cages were in every respect similar except that the floor of the cage was made of a removable sheet of wood: the object here being to favour the infection of the food grains by the droppings of the birds. The birds in one of these cages received a liberal diet of mixed grains as above; those in the others received milled rice only.

(b) Twenty-four pigeons were isolated in separate and new cages, each cage having the following dimensions: 1′ 6″×1′ 6″×1′ 6″. The bottom, as well as the sides, of these cages was of netted wire. Twelve birds so isolated received a liberal diet of mixed grains and sand, and the other twelve received milled rice only.

There were thus 36 control pigeons on mixed grains and 36 pigeons on milled rice. A further precaution against infection was taken by conducting the experiment in a large room wherein animals had not been previously confined.

(ii) The rice employed was a milled rice obtained locally. The milling had deprived it of its germ. About one grain in every ten, however, when tested by means of iodine solution, was found to show a minute speck of adherent pericarp which the milling had not completely removed.

The rice was fed to the pigeons in its raw state for a period of forty days, during which time only one case of polyneuritis occurred amongst 36 birds so fed; this case was well marked and exhibited pronounced degeneration of the sciatics. Consequently, from the forty-first day forward, the rice was autoclaved at a temperature of 130° C. for three-quarters of an hour.

(iii) All 72 birds were weighed weekly, and during the later period of the experiment their respirations and temperature were taken at the same time.

(iv) A separate history sheet was kept for each bird, and the symptoms from which it suffered and other details with regard to it were recorded minutely.

(v) When the morbid state from which the birds were suffering had progressed to the point of death, the temperature and respirations were recorded, the birds weighed, killed, and their organs examined bacteriologically. An immediate autopsy was performed with the minutest care. The brain, the thymus, the thyroids, the pituitary, the pancreas, the heart, the stomach, the liver, the spleen, the adrenals, the kidneys, the testicles, the ovary and the lungs were removed and weighed. Part, and in some cases the whole, of each organ was fixed and set aside for future histological study. A portion of the spinal cord, as well as the vagi and both sciatic nerves, were also removed and treated by Marchi's method.

2. *Duration of the Experiment*

The experiment commenced on the 29th April 1918 and terminated one hundred and eleven days later, when the last bird on milled and autoclaved rice died. Two of the 36 birds fed on rice and one control, having been found at autopsy to have tubercular disease, were excluded. All other controls remained in good health during this period.

3. *General Observations*

(i) INCUBATION PERIOD

The incubation period varied from 30 to 100 days, the average being 67·1 days. In males the incubation period was 62·6 days, in females 73·7 days.

It is invariably stated that the symptoms of polyneuritis appear in pigeons in from 15 to 25 days. I may say at once that this has rarely been my experience. Where infection, as a determining factor in the onset of symptoms, has been excluded by bacteriological examination of each bird, symptoms of disease have, with the exception of one experiment (in young growing birds), not appeared under 25 days even where milled and autoclaved rice, artificially fed to the birds, was used. On the other hand, a high percentage of birds may survive this dietary for very much longer periods. It will at once be argued that the rice I employed must have contained a sufficiency of protective substances to delay the onset of symptoms. In the present experiment this may to a certain extent have been true during the first 40 days; that is, before autoclaving was commenced; although one of the most severe and typical cases of polyneuritis occurred within this period. I consequently repeated the experiment in 12 birds which received only autoclaved rice from the commencement. In one case symptoms of disease appeared on the 30th day, in another on the 32nd day, in a third on the 34th, in a fourth on the 37th day. Of the other 8 birds one survived 59 days, a second 60 days and the remainder for periods ranging from 72 to 85 days. Two of these, artificially fed to the extent of one-fifteenth part of their body-weight of rice daily, survived for 73 and 74 days respectively. A considerable proportion of pigeons can, therefore, survive a diet consisting solely of rice, which has been subjected to a degree of heat far in excess of that reached in the process of cooking human food, for periods of 50 to 60 days.

I have found from further experiments, using pigeons whose ages were known, that in non-infected birds age is the chief factor in determining the onset of symptoms: these appear much earlier in young and growing birds.

(ii) DESTRUCTIVE ACTION OF HEAT ON 'VITAMINES'

A further point arises as to the destruction of accessory food factors by heat. My own experience has been that while subjection of milled rice to a temperature of 130° C. in the autoclave, for three-quarters of an hour, has in some cases appeared to hasten the onset of symptoms it has not invariably done so, all other factors having a deleterious influence on the health of the bird having been excluded when the test was made. I have at present 6 birds under experimentation which have been fed on autoclaved rice only for no less than 70 days, without having shown any signs of polyneuritis. I cannot help feeling that too great significance is often attached to the destruction of 'vitaminic' substances by boiling, and too little to other possible aetiological factors in the genesis of morbid states in the presence of the deficient dietary. It is often argued that differences in cooking account for the freedom from disease of certain classes of a given community using the same food; as, for example, in the case of 'ship beri-beri', where stokers frequently suffer more than do deckhands. While I do not deny that such may be the case, I consider this argument is invalid unless all other factors—and amongst these bacterial infections are of high importance—have been definitely excluded. I am aware of no case in which this has been done.

(iii) INFLUENCE OF SEX IN DETERMINING THE TIME OF ONSET OF SYMPTOMS

Of the 34 diseased birds, 20 were males and 14 were females. Of these the males died of the disease, or were killed when at the point of death, in an average of 67·9 days; the females in an average of 79·8 days. Males are, therefore, more susceptible to morbidity resulting from this form of food deficiency than are females—a fact which is in conformity with the incidence of beri-beri in the human subject. It is possible that this sex difference may be due to the fact that females eat less. This can only be cleared up by noting whether or not females artificially fed survive longer than males. This point is now under investigation. (Of 7 young pigeons artificially fed on autoclaved rice, 3 males died in an average period of 47 days; 4 females in an average period of 44 days. Their organs were sterile. Artificial feeding, therefore, seems to equalize the incubation period in the two sexes. This experiment appears to indicate that the quantity of starch consumed is a factor of considerable importance.)

(iv) INFLUENCE OF SEGREGATION

Of these 34 diseased pigeons, 11 (6 females and 5 males) were segregated in separate cages while 23 were congregated together in two large cages. The former took on an average 85 days to die of the disease and 80 days in which to acquire it, the latter 66 days to die of it and 61 days to acquire it. Allowing for the influence of sex, this difference is sufficiently marked to justify the conclusion that congregation favours the onset of symptoms. I consider this result to be in part due to the quieter life led by the isolated pigeons. In the retirement of their own cages their metabolic fires burn less briskly, their sexual desires, in the absence of the female and competetive male, are less ardent. Thus are conserved the resources of the endocrine glands on which so much of the morbid processes of deficiency disease is dependent. Were congregation, however, as in the human subject, to introduce factors which would impair or unduly tax the resources of these organs—as, for example, deficient oxygen supply, focal infections, malaria, dysentery, ankylostomiasis and the like—the beneficial influence of segregation would be more marked than the figures indicate.

(v) INFLUENCE OF CONTAMINATION OF FOOD BY THE BIRDS' EXCRETA

Twelve diseased birds which were confined in a single netted wire-bottomed cage died of disease due to the deficient diet in an average of 68 days. Twelve confined in a cage of similar size but with a wooden floor died from the same cause in 64 days. Infection from the birds' excreta may, therefore, be regarded as having possessed little or no influence in this particular experiment, due doubtless to the absence of any pathogenic organism capable of spread by such means.

4. *Clinical Observations*

Among the thirty-four cases under study three types of morbid state were recognized clinically:

(a) A state in which cerebellar symptoms predominated—seventeen cases.

(b) A state of polyneuritis without cerebellar symptoms—nine cases.

(c) A state of pronounced asthenia—eight cases.

Cases to which the term 'fulminating' could be appropriately applied have been confined in my series to those in which septicaemia was also present.

I propose to record here only such clinical observations as appear to supplement the published accounts of *polyneuritis columbarum*.

(i) ONSET OF SYMPTOMS

This is, as a rule, gradual but may occur with startling suddenness. For some days prior to the detection of any nervous symptoms the bird may be noticed sitting hunched up in its cage with ruffled feathers. Occasionally, however, a bird may one day appear well, apart from progressive weakness, and the next be taken with convulsive seizures in which it turns 'cart-wheels' backwards at periodic intervals up to the time of its death. Or a bird which for several days may have been sitting in a quiet corner with ruffled feathers, in a state of torpor, from which it can be roused to comparatively active and unhampered movement, may suddenly have a convulsive seizure and die. This is, however, rare. More common is it for a bird exhibiting a steadily increasing weakness and paralysis, which may have persisted for four or five days, to die suddenly in the night.

(ii) DURATION OF THE DISEASE

The duration of the disease is variable. Sudden death may occur while in a state of depressed health which, however, has presented no obvious features of paralysis; or asthenic cases may survive in a state of extreme feebleness for 10 to 12 days. In one case which exhibited polyneuritis without cerebellar symptoms, although it had occasional convulsive seizures, the bird survived for 15 days; in another for 21 days. This is, however, very exceptional. As a rule, the duration of the symptoms is 3 to 5 days.

It is usual for cases to develop the typical signs of polyneuritis first, and a day or two later those which are clinically referable to the cerebellum. In all probability had I refrained from killing any of the birds some of those which I have classed as 'polyneuritis' might have developed cerebellar symptoms. On the other hand, birds may survive the symptoms of polyneuritis without developing cerebellar symptoms for as long as 15 to 21 days in rare cases.

(iii) SUDDEN DEATH

Five of these thirty-four cases are noted to have died suddenly: one without any premonitory warning of danger, in a convulsive seizure. Four others were of the asthenic type, exhibiting no symptoms other than those which might reasonably be attributed to a progressive weakness; in those cases the symptoms of neuritis may have been present but masked by the asthenia. All of these were found at autopsy to have adrenal glands much larger than the average of control birds, while two had in addition well-marked hydropericardium. Sudden death, therefore, is likely to occur in consequence of convulsions or to be associated with hydropericardium and adrenal enlargement.

(iv) CONVULSIONS

Convulsive seizures have been a very common accompaniment of the morbid states observed in this series of birds. They are limited, as a rule, to cases of the cerebellar type: very rarely they occur without any other appreciable evidence of nervous disease; while occasionally they are present in cases which have been grouped as 'polyneuritis'.

The cerebellar character of these seizures is usually well marked: the bird turns 'cart-wheels' backwards either in a direct line, more commonly in a circle (major attacks), or, while standing erect, it revolves slowly in a circle to one or other side of the body (minor attacks). These attacks are readily produced by stimulation. They are periodic in their occurrence, the periodicity varying in different birds. Seizures may occur every ten to fifteen minutes or at intervals as long as two hours. Major attacks are usually associated with astasia. Birds exhibiting the minor attacks are able to stand. A bird may be standing huddled up in a position of rest when suddenly it will start moving round and round in a circle, its feet acting as the centre of the circle of its rotation. Stimulation will often induce it to move in this curious way, so typical of cerebellar disease. Tremors of the wings, of the head or of the eyelids were frequently noted.

The periodicity of these seizures has reminded me forcibly of the periodicity of attacks of tetany, although the fits do not themselves resemble those of this malady. Nor is there any clinical reason to suspect the disease of the parathyroids as a causal factor in their origin. Close observation, however, has led me to believe, on clinical grounds, that the attacks may be due to the accumulation in the body of the toxic products of disordered metabolism, and be comparable to those of tetany which result from the accumulation of guanidine in consequence of disease of the parathyroid glands.

It is a point of considerable practical significance that a diet deficient in certain accessory food factors is capable of giving rise to convulsions, either alone or associated with other evidences of disease.

(v) OTHER NERVOUS SYMPTOMS

'Retraction of the head' is a frequent symptom. More rarely the head may be inverted, or tucked underneath the breast, the back of the head touching the floor and tending to describe semicircles thereon. These symptoms, together with the inco-ordination, which is such a marked feature, I regard as being due to changes in the cerebellum or in cell-groups within its sphere of influence. On clinical grounds alone I consider that the term 'polyneuritis' as applied to all these cases is inapt. The nervous symptoms are not due to a peripheral neuritis but to an impairment and loss of function, or to destruction of a proportion of cells of the central nervous system. Functional impairment of cells and neurones is, I believe, a frequent manifestation of morbidity resulting from a dietary of milled rice, whilst destruction of nerve cells and neurones is much less common.

(vi) SENSATION

Sensation is often greatly impaired. If a test-tube containing very hot water be applied to the foot the member may not even be withdrawn from its contact. The sensations of heat and cold are greatly delayed or may be completely in abeyance. If a thick platinum wire be heated red-hot and applied to the pad of the foot, it may not be withdrawn until the cutaneous tissues are deeply scorched. Tactile sensation also seems to be impaired; the prick of a needle on the foot often eliciting little or no muscular protest.

(vii) SPECIAL SENSES

It has appeared to me also that in some few cases the sense of sight is impaired. If an object such as the tip of the finger be approximated to the eye it is not until the cornea is actually touched that an attempt is made to withdraw the head. On the other hand, cases have been met with in which the eye appears hypersensitive to light and touch; more commonly eye symptoms are wholly absent.

Impairment of the function of deglutition is a frequent symptom. If the bird be inverted the contents of the crop may run out of the mouth. Again the bird may hasten with faltering step to a much-desired grain and be unable to pick it up or to swallow it. If the grain be put into its mouth it may succeed in swallowing it only after many forced movements. A very considerable proportion of birds eat greedily to the last; freshly ingested rice is often found in the crops and stomachs of birds after death.

(viii) DROPSY

The clinical recognition of dropsy or of serous effusions is very rare. I have met with dropsy of the feet and subcutaneous tissue in two cases only. Effusion into the serous sacs or oedema recognizable at autopsy is of comparatively frequent occurrence. It will be referred to when considering the post-mortem findings in these cases.

(ix) RESPIRATION

A series of 129 observations has revealed the fact that the respirations of healthy pigeons at this altitude, 6,000 feet, average about 60 per minute. In diseased birds the respirations become progressively deeper and less frequent with the progress of the morbid state, and may reach the low figure of 18 per minute. Frequently the bird exhibits respiratory movements suggestive of ‘air-hunger’. The beak is then held open and forcible gasping movements occur at the rate of 20 to 22 per minute. These are not always synchronous with the rise and fall of the abdomen, which may be slightly higher in rate. More rarely the abdominal movements are indicative of disordered diaphragmatic action, probably resulting from functional derangement of the phrenic nerve. Clearly there is impairment of the respiratory exchanges in these cases. The progressive deepening and slowing of the respirations is highly suggestive of acid-irritation of the respiratory centre. Birds subjected to prolonged inanition, which is known to give rise to acidosis, did not exhibit these respiratory phenomena in such marked degree.

(x) BODY TEMPERATURE

The body temperature in the healthy pigeon, as taken in the cloaca, is found to vary considerably throughout the course of the day. Possibly the constant presence of Halteridium infection in control and diseased birds alike, may account in some measure for this variation. In apparently healthy birds the diurnal range may be between 103·8 and 109·8° F. The average of 129 observations, made in the forenoon in thirty birds, was 107° F.

One of the most characteristic features of the morbid state is the steady fall of body temperature; it may be reduced to 98° or 97° F., and in rare cases even to 96° F. A similar fall of body temperature occurs in pigeons subjected to prolonged inanition.

Diseased birds in which the temperature is higher than 104° F. just prior to death will almost certainly prove to be infected. This is indeed the most ready means of separating infected from non-infected birds. This observation is one of considerable clinical significance in regard to human beri-beri. Where the disease is due to lack of accessory food factors alone, the patient should have no fever. Should fever also be present, some source of infection is likely to be found.

(xi) THE BLOOD

Blood-counts have been made just prior to death in 15 control and in 11 diseased birds. The red blood-count in healthy birds varies within wide limits as, for example, between 2,720,000 and 4,752,000 per c.mm. Doubtless the varying degrees of Halteridium infection account in some measure for this variation; this being so the influence of the parasite will be at least equally well marked in diseased birds. In these the variations of the red blood-count are more considerable, ranging from 1,232,000 in one case to nearly 3,452,000 in another. The average of both series indicates a tendency to diminution of the nucleated red cells of the blood amounting to over 25 per cent.

No marked diminution or alteration in proportion of the white cells was definitely established although such is believed to exist. This was due in part to the unusual difficulty in their estimation owing to the frequent presence in pigeon blood of nucleated cells other than red cells or leucocytes. The estimation of those cellular elements involved a preliminary cytological study of normal pigeon blood which I had not the time to undertake. This point is one which requires investigation. I was unable to establish any connection between the severity of the Halteridium infection and the occurrence of beri-beri.

(xii) THE FAECES

Diarrhoea is a frequent symptom. The discharges are often very fluid and may be emerald green in colour. *B. pyocyaneus* was isolated in two cases from such excreta. Microscopical examination of the faeces shows the frequent presence of tapeworms' or other eggs. The mass of the faeces is made up of bacteria with undigested or partly-digested starch. The diarrhoea may be due to microbic fermentation of mal-digested starch. Such fermentation will result in an excess of mineral and organic acids in the intestines. It may be assumed, therefore, that the absorption of these will lead to an excess of acids in the blood. This observation suggests that acidosis is one of the consequences of such a dietary. The point will be referred to again when dealing with the post-mortem findings in the pancreas. In cases cured by 'vitaminic' extracts the disappearance of profuse diarrhoea may take place with extraordinary rapidity. So striking is the improvement that one is led to think that intramuscular injections of 'vitaminic' solutions (as of the yolks of eggs) might prove of value in those cases of acute or obstinate diarrhoea so frequently associated with malnutrition, from whatever cause arising.

(xiii) BODY-WEIGHT

The great loss of body-weight resulting from a diet of milled rice has been so frequently recorded in minute detail that it appears to be unnecessary to add further to the volume of statistics on this point. I doubt, however, whether previous records have always excluded microbic agencies as factors in materially increasing this wasting. It will suffice to illustrate the loss of weight by two diseased and two control birds of the same sex and weight. These are sufficiently representative of the classes to which each belongs.

5. *Morbid Anatomical Observations*

(i) GENERAL APPEARANCE OF DISEASED BIRDS

On coming to autopsy the great general wasting is very striking. The skin is slightly darker than in control birds, due to the disappearance of all subcutaneous fat: no petechiae or cutaneous ecchymoses—although the surface and deep veins are often engaged—have been observed. The neck is thin, the breast muscles greatly wasted so that the sternum projects like the keel of a racing yacht. In a very small percentage of cases (one in thirty-four) there was present slight subcutaneous oedema especially in the region of the abdomen and the groins. In twelve cas the flesh was observed to be of normal tint and to present, apart fro the great wasting, no macroscopical appearance which could be r garded as notably different from that of healthy birds. In two a curiou mottling of the muscles was observed, darker and lighter areas alterna ing with each other. In eight cases the muscles were of a uniform dar ish red hue, notably darker than that observed in control birds. In thr others, and these showing oedema in some form, the tint of the fles was very dark, approaching that characteristic of septicaemic case The fact that septicaemic states impart to the skin and muscles differe appearances to those in which the tissues are shown to be sterile is considerable practical importance. One can tell almost at a glan which birds have sterile organs and which have died of septicaemia. has not been observed that the muscles were invariably damp. Indee oedema of the muscles was rare, but in the cases in which it was prese (three in thirty-four) it was a marked feature: in one case being s marked as to necessitate the use of swabs in order to clear the field operation of the fluid exuding from the tissues.

Here I should like to point out that while the general pathologic features of cases of *polyneutitis columbarum* are likely to be the same i all countries where experiments on pigeons are carried out, they nee not necessarily be identical. The chief causes of variation in morbi anatomical appearances are undoubtedly infectious agencies. The i fluence of these cannot be wholly excluded, for although the sterility the blood and organs may be demonstrated the effects of gastro-inte tinal infections and of intestinal parasites cannot be discounted; thes will most certainly vary with locality, climate, temperature, previou food and what not. The importance of realizing this cause of variatio in results has been prominently brought to my mind in comparing thos I obtained in the north of India, in 1914, with those obtained in th south in 1918. It is, unfortunately, not unusual for observers in differe parts of the world finding that their observations differ from those workers in other countries to conclude that the observations of th latter are faulty, without taking due count of other factors which ma have materially influenced the results observed. I notice, for exampl that three or four experimenters report their failure 'to confirm' m finding with regard to the occurrence of *B. suipestifer* in certain cases *polyneuritis columbarum* observed at Kasauli, India, in 1914. They hav missed the point however: it is that this organism having been prese in these cases certain results were observed of important aetiologic significance. Its presence was no doubt fortuitous—I have, myself, n regarded it as other than such—but none the less instructive. I woul emphasize that differences in the results of experienced experimenters in different parts of the world are worthy of the most careful consideration, since the explanation of these differences may reveal the secrets for which we are searching.

In the accompanying table (p. 94) are shown the average weights of the internal organs of 35 control pigeons, and of 34 pigeons which developed morbid states in consequence of a diet consisting solely of milled and autoclaved rice. The weighing was done immediately on removal of the organs from the body; the autopsy, except in a few cases, was performed immediately after death. Attention to this point is of great importance especially when dealing with such organs as the adrenals, the adrenaline content of which is so liable to rapid oxidation and decomposition after death. In all 69 cases the heart's blood and internal organs were sterile.

From a study of the weights, in the table, it will be seen that the organs fall into three classes:

(a) Those which remain unchanged: the pituitary;

(b) Those which undergo hypertrophy: the adrenals;

(c) Those which undergo atrophy: the thymus, testicles, spleen, ovary, pancreas, heart, liver, thyroids, kidneys, brain.

The similarity of the changes in size of those organs to those which occur in inanition is very striking.

These organs will now be considered in the order named:

(ii) THE PITUITARY GLAND

Removal of this organ intact is, in the pigeon, a matter of considerable difficulty. The anterior portion, which is of the size of a green mustard seed, shells out of its bony casing with ease, but in the process of dissection it is very difficult to retain its connection with the posterior portion. The same technique for its removal having been followed throughout the whole series of 69 birds, without any foreknowledge of the probable nature of the findings, the weights given may be regarded as sufficiently accurate; although it is to be recognized that in weighing an organ so minute sources of error are apt to arise. In all cases the gland was dried on filter paper before weighing, as indeed were all the organs of the body.

(a) *Anatomical Note*

The average weight of the pituitary in the male control pigeon is 5·3 mg.; in the female 5·9 mg. As estimated per kg. of body-weight, the pituitary tissue amounts in males to 18·3 mg. and in females to 22·1 mg. In healthy pigeons, therefore, the pituitary is considerably heavier in

Weights of organs of control pigeons, of those on rice diet, and of pigeons subjected to inanition: weights calculated in terms of original body-weight of birds; all weights in mg.

Organs	*Controls*		*Rice*		*Inanition*	
	Average weight	*Weight per kg.*	*Average weight*	*Weight per kg.*	*Average weight*	*Weight per kg.*
	Males		*Males*		*Males*	
Thyroids	24·7	84·7	22·5	76	—	—
Liver	6,168	21,136	5,178	17,540	—	—
Spleen	339·2	1,162	87·2	295	—	—
Heart	3,084	10,568	2,250	7,621	—	—
Kidneys	1,594	5,464	1,563	5,298	—	—
Adrenals	29·2	100·3	42	139·5	—	—
Thymus	678	2,324	14	47	—	—
Testicles	1,355	4,643	119	401·5	520	1,857
Pancreas	949·7	3,254	615	2,082	—	—
Brain	2,010	6,910	1,986	6,843	—	—
Pituitary	5·3	18·3	5·8	19·6	—	—
Stomach	5,716	—	3,514	—	—	—
	Females		*Females*		*Both Sexes*	
Thyroids	22·6	85·5	21·2	75·8	15·8	59
Liver	5,405	20,371	5,556	19,793	3,961	14,900
Spleen	284	1,071	71	252	89·5	336·6
Heart	2,713	10,228	2,139	7,621	1,626	6,119
Kidneys	1,480	5,578	1,543	5,500	1,164	4,379
Adrenals	24	90	41·9	149	33·3	125·4
Thymus	318	1,201	0	0	53·3	209
Ovary	253	953	85·7	305	67·5	260
Pancreas	898	3,383	562	2,004	443	1,666
Brain	1,861	7,015	1,862	6,635	1,889	7,107
Pituitary	5·9	22·1	6·3	22·4	4·1	15·6
Stomach	5,716	—	3,514	—	4,163	—

females than in males. In diseased birds, the average weight in males is 5·8 mg., in females 6.3 mg.; as estimated per kg. of body-weight the pituitary tissue in diseased males amounts to 19·6 mg., and in females to 22·4 mg.

There is thus, generally speaking, no noteworthy alteration in the weight of pituitary tissue in consequence of the dietetic deficiency in females, whereas in males it shows a slight tendency to increase. While this finding is correct when the total weights of pituitary tissue in the four categories are compared, individual cases, in both males and females, are often found to have pituitary glands well above the average weight.

The tendency to enlargement of this organ may be of some significance in connection with the hypertrophy of the adrenals, in view of the fact that the secretions of the posterior portion of the pituitary and of the adrenals mutually facilitate each other's action on the muscular coats of the blood-vessels although their mode of action differs.

It appears probable that under conditions of 'vitaminic' deficiency the resources of both the pituitary and the adrenals are taxed to the utmost in an endeavour to maintain vascular tone.

(iii) THE ADRENALS

The most remarkable result emerging from this research is the demonstration of the hypertrophy of the adrenals which results from a dietary deficient in 'anti-neuritic vitamines'. So far as I am aware, it is a finding which has not hitherto been recorded.

(a) *Anatomical Note*

In the pigeon the adrenals are situated in the middle line of the body, between the upper poles of the kidneys. They are closely applied to the spinal column to which they are bound down by areolar tissue. They lie side by side, and separated only by the main vascular trunks. The tissues of the adrenals and kidneys are not continuous or intermingled one with the other but are divided by a space, filled with loose areolar tissue, varying in width from 0·2 to 0·5 cm. In shape these organs are pyriform or roughly triangular; the base being uppermost as the bird lies on the dissecting table. They are of a yellow-ochre or dull-yellow colour, and average about 0·6 cm. long by 0·4 cm. at their widest part: at the upper or broad extremity they are about 0·2 cm. thick. One organ is occasionally slightly larger than the other; when this is the case the right is commonly the larger of the two. Their consistency in health is quite firm. In the male they are closely adherent to the posterior and inner border of the testicles which overlie them. In removing them they should be dissected up from the spinal column together with the testicles and the dissection completed under the dissecting microscope. In the female the ovary overlies the left adrenal but rarely the right; their removal is difficult and can only be satisfactorily accomplished by gently scraping the ovarian tissue from off the gland's surface. Both organs should then be removed together by dissecting them, with the vascular trunks, from off the spinal column and completing their separation under the microscope.

On removing the liver, stomach, and intestines, the enlargement of the adrenals in diseased birds is at once apparent, especially so as the great atrophy of the reproductive organs leaves them exposed to view.

Nothing is more remarkable in the male than the appearance of the atrophic testicles and the neighbouring hypertrophic adrenals. In adult healthy birds the large testicles are fifty times the size of the adrenals, whereas in diseased birds the latter organs may actually be larger than the former.

In control male birds the weight of the adrenals ranges between 18 and 49 mg.; any enlargement of the organs over this limit is highly suggestive of septicaemic processes. The average weight in control males is 29·2 mg., or 100·3 mg. per kg. of body-weight. In only 2 cases out of 19 did the adrenals weigh over 40 mg. These were amongst the first birds to be autopsied, and subsequent experience has taught me to be very doubtful of the freedom of (control) birds from infections where the adrenals weigh as much as 40 mg.

In control female birds their weight ranges between 11 and 37 mg.; the average weight being 24 mg., and per kg. of body-weight 90 mg. In the present series of 35 healthy birds, therefore, the adrenals were slightly larger in males than in females.

In diseased males, on the other hand, the extremes of weight of these organs were 27 and 70 mg., the average being 42 mg., and per kg. of body-weight 139·5 mg. In 10 cases out of 19 the adrenals weighed 40 mg. or over. In diseased females the range of weight lay between 18 and 91 mg.; the average being 41·9 mg., and per kg. of body-weight 149 mg. Six female diseased birds had adrenals of 40 mg. or over.

These organs in diseased birds present very characteristic appearances when contrasted with those of healthy birds. They are swollen, prominent and of a yellow-red or reddish-brown colour, often hyperaemic, diffluent and easily torn, frequently weighing less than their size leads one to expect. Much of the yellow-ochre colour of health has disappeared or may only be found in patches.

(b) *Histological Observations*

The histological study of the sixty-six pairs of diseased and control adrenals which I have set apart for examination is in itself a prolonged investigation. Up to the present I have examined only ten control glands and ten from diseased birds, and these after chrome-salt fixation and staining by Delafield's or Mann's stain. Those glands treated by special methods for the study of cortical lipoids, etc., have not yet been sectioned. From this limited number of examinations the impressions I have derived (and tnese are subject to modification by more detailed study) are: (1) The enlargement is not the result of hyperaemia; the organs often show histological evidences of congestion, which may be very marked in the larger glands, but pronounced congestion appears to result from venous stasis arising subsequent to the initial enlargemen- of the organ. (2) In some of the larger glands examined intense congestion had caused destructive changes in the glandular tissue; this was especially noticeable at its central part, the peripheral areas retaining much of their normal characters. (3) There appears to be little or no diminution of the chrome-staining granules of the medullary columns except in very large and hyperaemic glands. (4) The cortical columns appear to form a greater proportion of the section in diseased than in healthy birds. (5) The nuclei of both medulla and cortex are fewer in number, area for area, in the diseased cases. (6) The nuclei often appear more vesicular, larger and frequently more shadowy in form, while cells without nuclei, or containing only shadow nuclei, are commonly met with. (7) Some cells of the cortex show small uniformly dark-staining nuclei which are in marked contrast to the more vesicular nuclei of the normal cortex. (8) Some diseased glands show many cells with brightly staining eosinophile granules when stained by Mann's stain. (9) Many cells in both cortex and medulla appear to differ but little from normal. (10) Sections of the organ from healthy birds have occasionally shown, most clearly, various stages in the process of secretion in the cortical cells; some being packed with granules, others, lying side by side with them, having an empty cytoplasm. These appearances seem to indicate that the cortex secretes a substance which is discharged into the medullary areas of the gland—a point concerning which there is much difference of opinion. (11) Sections have frequently shown sympathetic nervous tissue closely adherent to the periphery of the gland; with the stains used, some of the large cells of these sympathetic ganglia have presented appearances—changes in the nuclei and diffuse staining of the cell-body—indicative of degeneration.

A more detailed study of the cortical lipoids of the adrenals is obviously called for. These organs are said to be the chief source of body lipoids. Since these substances are intimately concerned with the nutrition of the myelin of medullated nerve fibres, it may be presumed that the adrenal cortex will undergo some notable change in beri-beri.

(c) *Kymographic Observations*

With the assistance of Colonel Cornwall, to whom I am much indebted, I have been able to demonstrate, by kymographic observations of the arterial blood-pressure in sheep, that the enlargement of the adrenals is a true hypertrophy, being accompanied with a great increase of the adrenaline content of the organs.

The adrenals used in these observations were as far as possible removed immediately after death so as to avoid oxidation of their adrenaline. They were then weighed and emulsified in a sterile mortar with about 5 c.c. of 0·85 per cent saline solution. The emulsions were injected into the left jugular veins of sheep under ether anaesthesia; the kymographic tracing being taken from the right carotid. The following conclusions emerge from these kymographic observations:

(1) Sheep vary greatly in their susceptibility to adrenaline administered intravenously. Single observations in different sheep are not strictly comparable.

(2) The averages of five observations in which the adrenals of healthy birds were employed, and of six in which the adrenals from cases of avian beri-beri, were used are approximately as follows:

(a) 20 mg. of healthy adrenals caused a rise of blood-pressure of 21 mm. of Hg. in 38 lb. sheep.

(b) 50 mg. of beri-beric birds' adrenals caused a rise of blood-pressure of 58 mm. of Hg. in 40 lb. sheep.

The adrenaline content is thus proportionate to the increase in size of the glands in these cases of beri-beri.

(3) There appears to be no retention of adrenaline in the enlarged glands. Its quality also appears to be little altered.

(4) Cases of pigeon beri-beri with oedema have larger adrenals, containing more adrenaline than cases without oedema. (See *Analyses*, tables, p. 101 and p. 104.) The rise in blood-pressure which follows the injection of these organs in emulsified form is correspondingly greater.

(5) The greater part of the adrenaline content of these organs is destroyed by oxidation within seventy-two hours after death.

(d) *Causes of Adrenal Hypertrophy*

It seems clear that the adrenals hypertrophy for want of 'vitaminic' substances since they do so both as a result of inanition and of a polished rice dietary. Endocrinology provides another striking illustration of such hypertrophy, namely, that of the thyroid for want of iodine. The thyroid hypertrophies either because of the lack of iodine in the food or because of its imperfect assimilation, due to microbic action in the gastro-intestinal tract, and most commonly when both factors operate together. My researches with regard to beri-beri are leading me to a like conclusion concerning the adrenals: these enlarge for want of 'anti-neuritic vitamines' in the food and probably also in consequence of the inadequate assimilation of these substances owing to microbic or parasitic action in the gastro-intestinal tract, or for both reasons. Here I would again direct attention to what I have called the minor manifestations of 'vitaminic' deficiency. It is clear that if such deficiency—as opposed to complete deprivation of these substances—leads to abnor-

Effects on arterial blood-pressure of intravenous injections of emulsified adrenals from healthy and beri-beric pigeons into sheep; controlled by pure adrenaline.

Pigeon	*Weight of Adrenals in mg.*	*Weight of Sheep in lb.*	*Rise of Blood-pressure in mm. of Hg.*	*Other Details*	
77	32	46	12	Healthy bird	
112	39	47	38	Beri-beric bird: no oedema	
86	45	43	38	,, ,, oedema	Same sheep
87	49	43	42	,, ,, ,,	
155	37	39	38	,, ,, no oedema	Same sheep
—	—	39	56	0·1 mg. of adrenaline	
128	18	32	24	Healthy bird	Same sheep
130	18	32	28	,, ,,	
162	15	47	32	,, ,,	Same sheep
85	43	47	26	Beriberic bird: oedema: dead 72 hours: adrenaline oxidized	
83	29	47	10	Beri-beric bird: no oedema: dead 72 hours: adrenaline oxidized	
—	—	47	64	0·1 mg. of adrenaline	
158	16	35	8	Healthy bird	Same sheep
116	72	35	72	Beri-beric bird: oedema	
—	—	35	34	0·1 mg. of adrenaline	
111	53	33	124	Beri-beric bird: oedema	Same sheep
—	—	33	82	0·1 mg. of adrenaline	

mal action of the adrenal glands we have a key to many aetiological problems which have so far baffled us.

Not only do the adrenals enlarge for want of 'vitaminic' substances but, I have reason to believe, they return to a more normal volume almost immediately these substances are provided. One pigeon developed the cerebellar type of avian beri-beri after nineteen days' consumption of a diet of autoclaved rice. So severe were the symptoms that the bird was observed to have convulsive seizures, turning 'cart-wheels' backwards at intervals of five minutes or so, while it suffered from profuse and persistent serous diarrhoea. It was treated by injection into the crop of the 'vitaminic' extract of the yolks of four eggs. The bird made a dramatic recovery within twenty-four hours—a recovery which included not only complete cessation of the fits, but disappearance of the symptoms of polyneuritis, with the exception of a high-stepping gait, and cessation of the diarrhoea. It was most remarkable to see the bird fly round the laboratory alighting on convenient objects with facility. It was replaced in its cage and the diet of autoclaved rice continued. With the exception of the slight alteration in gait, the bird appeared to be comparatively well during the next four days, sitting on its perch with ease and even tucking one foot under its breast feathers while so perched. It died suddenly at the end of four days and presented many interesting features at autopsy. The bird had obviously had an extensive hydropericardium since the sac-wall was quite opaque and collapsed like a half-empty bag over the atrophied heart. The sac still held 1 c.c. of clear fluid. The adrenals were only 25 mg. in weight—a circumstance so unusual in cases of wet beri-beri that I have been led to think not only was the serous effusion disappearing, as did the serous diarrhoea, but the adrenals had diminished in size to a normal volume in consequence of the injection of 'vitaminic' extract into the crop. This is an isolated observation: one cannot conclude from it, though one may speculate concerning it.

(e) *Object of the Adrenal Hypertrophy*

The object of the adrenals' hypertrophy is difficult to understand, since our knowledge of their function is still so nebulous.

Although absolute proof of hyperadrenalinaemia can only be afforded by demonstrating an excess of adrenaline in the venous blood from the adrenals, yet the evidence, I think, justifies the presumption that adrenaline enters the blood-stream in excess. There, it may be presumed, it exerts its physiological action in an endeavour to maintain the tone of the sympathetic system and of the cardiovascular muscles, to provide the requisite chemical stimulus for the activation of the vegetative organs of the body, and, in correlation with the pituitary, the pancreas, the liver and the thyroid, to control the metabolism of carbohydrates. These at least are the functions with which the medulla's secretion is credited in the present state of our knowledge. It is evident that their exercise will become more and more difficult, more and more imperative as the process of slow starvation goes on. Certain it is that despite the increased production of adrenaline progressive cardiovascular depression occurs in avian beri-beri.

It will have been noted that the pituitary gland does not share in the general atrophy of the body tissues resulting from a dietary of autoclaved rice although it does so in inanition. One must be very cautious in concluding as to the occurrence of atrophy or hypertrophy of an organ which is at once so small and so difficult to remove intact. Therefore, I say only that in this series of cases it did not share in the generalized atrophy of the body tissues.

Weights of the adrenal glands in thirty-one cases of experimental beri-beri (first series) in adult pigeons with special reference to the occurrence of oedema

No. of Pigeon	*Sex*	*Original Weight (gm.)*	*Weight of Adrenals (mg.)*	*Weight of Adrenals per kg.*	*Oedema*
14	Male	270	35	170	No oedema.
16	,,	340	50	147	1·5 c.c. of fluid in pericardium.
17	,,	270	43	159	No oedema.
52	,,	340	31	91	,, ,,
55	,,	290	27	93	,, ,,
22	,,	300	41	136	,, ,,
37	,,	250	29	116	,, ,,
45	,,	275	33	120	,, ,,
46	,,	340	37	108	,, ,,
48	,,	275	53	192	2 c.c. of fluid in pericardium.
43	,,	260	56	215	No oedema.
40	,,	300	33	110	,, ,,
24	,,	300	30	100	,, ,,
53	,,	260	40	153	,, ,,
58	,,	340	54	158	Oedema, abdomen and groin: ascites: hydropericardium.
47	,,	330	70	212	Marked oedema of tissues.
23	,,	280	43	153	2 drops of fluid in pericardium.
50	,,	290	36	124	No oedema.
19	Female	220	32	145	,, ,,
18	,,	270	37	137	,, ,,
21	,,	280	18	64	,, ,,
39	,,	350	22	63	,, ,,
42	,,	280	47	168	2·5 c.c. of fluid in pericardium.
13	,,	260	25	96	No oedema.
54	,,	300	65	216	,, ,,
51	,,	250	35	140	,, ,,
60	,,	240	62	258	2·5 c.c. of fluid in pericardium.
15	,,	280	38	135	No oedema.
41	,,	310	50	161	2·5 c.c. of fluid in pericardium.
57	,,	290	91	314	13·5 c.c. of fluid in pericardium.
56	,,	300	42	140	No oedema.
					NOTE. In five cases of *polyneuritis columbarum* in this series of thirty-six, the adrenals were not weighed in three, while two are excluded for other causes.

Analysis. In 13 cases of avian beri-beri, the weight of the adrenals per kg. of body-weight was 147 mg. or over; weight of the organs having been calculated against the original body-weight of the birds. Of these 9 had oedema in some form, or about 70 per cent. One hundred per cent of cases having oedema had adrenals of 147 mg. per kg. or over. Average weight of adrenals per kg., in control pigeons, 95 mg., in dry beri-beri, 127 mg.; in wet beri-beri, 196 mg.

There is considerable reason to believe that the excess of adrenaline poured into the blood-stream in beri-beri causes a state of tonic contraction of certain arterioles, during the earlier phases of the morbid process—a state which one would expect to be succeeded by vaso-motor collapse as the adrenals begin to fail. 'Yamagiwa also thought he found changes in the blood vessels, particularly in the media of the arterioles. In preparations of nerves, muscles and kidneys, he always found that the walls of the arterioles were thickened, and the lumen narrowed, and he believed that this was the essential change in beri beri. Thus he says: "The essence of Kakke consists in the increased resistance which occurs in the systemic and pulmonary circulation as a result of the contraction of the arterioles." The other changes, including the degeneration in the nerves, are only secondary to this primary alteration in the blood-vessels.'[1] Unless our whole conception of the adrenals' function is incorrect, the hypertrophy and hyperaction of these organs would appear to afford an adequate explanation of Yamagiwa's histo-pathological observations.

(f) *Oedema and the Genesis of Wet Beri-beri*

A fact as remarkable as the general tendency to adrenal hypertrophy in beri-beri is this: If adult pigeons fed on autoclaved rice have adrenals weighing 43 mg. (147 mg. per kg. of body-weight) or over, 70 per cent of them have oedema in some form: usually hydropericardium, rarely ascites, oedema of muscles or lungs. Further, 100 per cent of pigeons suffering from oedema have adrenal glands weighing 147 mg. per kg. of body-weight or more (table, p. 101). These facts appear to me to be more than coincidences. I am led, therefore, to surmise that an intimate and causal connection exists between the hypertrophy of the adrenals and the origin of oedema.

Professor Starling has classified the factors concerned in the causation of dropsy as follows:

I. Factors causing increased transudation:

(1) increased intracapillary pressure, especially that produced by venous obstruction, vaso-dilation and plethora being factors of minor importance;

(2) increased permeability of the vessel walls, produced by local irritants, malnutrition, or poisons circulating in the body generally;

(3) Hydraemia.

II. Factors causing diminished absorption, either by lymphatics or blood-vessels.

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[1] Quoted from Vedder's *Beri-beri*, 1913.

Of these two classes the first is by far the more important. In beri-beri, whether experimentally produced or naturally acquired, we have a condition of chronic malnutrition which is certainly associated with the circulation of the harmful products of a highly abnormal metabolism, if not also—in some cases of the disease at least—with the products of abnormal bacterial activity. To these is added progressive cardiac asthenia and an hypertrophy of the adrenal glands, with the presence in the blood-stream of amounts of adrenaline largely in excess of those of health. This excess presumably gives rise to the state of tonic contraction of the peripheral arterioles described by Yamagiwa. Thus are completed the conditions necessary for the occurrence of oedema: increased intracapillary pressure, malnutrition, and metabolic poisons.

Since, however, oedema is not invariably present under these conditions, other factors must exist which aid in determining its occurrence. Of these youth is one (see table, p.104); individual peculiarities of metabolism and of cardiac disorder are doubtless others.

I conclude, then: (1) that disorder of the adrenal glands and malnutrition of the tissues are the main factors concerned in the production of oedema in both inanition and beri-beri; and (2) that wet beri-beri and dry beri-beri are essentially the same disease but differing in the degree of derangement of the adrenal glands.

This account of my researches had been written and the above conclusions arrived at when I determined to commence a further series of experiments to confirm or disprove them. Young pigeons averaging about six months in age were similarly fed on autoclaved rice only, some of them being forcibly fed to the extent of one-fifteenth part of their body-weight of rice daily. Up to the present time twenty pigeons so fed, in which the blood and internal organs were demonstrated to have been sterile, have developed beri-beri. The results in these cases, with respect to the size of the adrenal glands and the occurrence of oedema, are shown in the table on p. 104.

These findings amply confirm the conclusions already arrived at as to the close association of oedema with massive hypertrophy of the adrenal glands. It will be observed that the number of cases in which oedema was present in this second series is extraordinarily high, amounting to 75 per cent. Such a result was wholly unexpected, and is to be accounted for, I think, by the fact that the birds employed in this second series were all about six months old, whereas those in the first series were two years old or over. In the absence of any other explanation I am led to the conclusion that young and growing pigeons are much more liable to suffer from oedema than older birds.

Weights of adrenal glands in twenty cases of avian beri-beri in young pigeons (second series), with special reference to the occurrence of oedema

No. of Pigeon	*Sex*	*Weight Before Experiment (gm.)*	*Weight After Experiment (gm.)*	*Weight of Adrenals (mg.)*	*Weight of Adrenals per kg. (mg.)*	*Oedema*
83	Female	255	180	29	113	No oedema
85	,,	210	155	43	204	Hydropericardium: 3·5 c.c.; slight oedema at auriculo-ventricular junction of heart
86	,,	250	190	45	180	Hydropericardium: 0·25 c.c.
87	,,	215	165	49	228	,, 0·5 c.c.; marked oedema at auriculo-ventricular junction of heart
88	,,	235	190	45	191	Hydropericardium: 0·25 c.c.
107	Male	225	190	65	254	,, 3·5 c.c.; slight ascites; oedema of lungs
111	,,	245	140	53	216	,, one drop only; well marked oedema at auriculo-ventricular junction
112	Female	240	170	39	162	No oedema
116	Male	230	145	72	313	Hydropericardium: 1 c.c.; marked oedema at auriculo-ventricular junction of heart
121	Female	245	140	40	163	No oedema
119	,,	200	130	70	350	Hydropericardium: 2 c.c.; oedema of lungs; well-marked oedema at auriculo-ventricular junction of heart
146	Male	240	175	35	145	No oedema
143	,,	210	120	47	228	Oedema of lungs
155	,,	270	150	37	140	No oedema
108	Female	215	145	58	270	Hydropericardium: 7 c.c.; oedema of lungs; muscles very moist
109	,,	220	130	60	272	Hydropericardium: 0·5 c.c.; blood stained with clot; oedema of lungs
110	Male	240	150	68	283	Hydropericardium: 1·5 c.c.; well-marked oedema at auriculo-ventricular junction of heart
148	,,	240	180	54	225	Hydropericardium: 0·5 c.c.
140	,,	230	190	52	226	,, 0·25 c.c.; intense oedema at auriculo-ventricular junction of heart
150	,,	290	180	68	234	Hydropericardium: 0·5 c.c.; slight oedema at auriculo-ventricular junction of heart.

(iv) THE THYMUS

(a) *Anatomical Note*

In pigeons the thymus consists of a chain of glands, resembling a string of sausages stretching from the base of the skull to the entrance to the thoracic cavity, and terminating commonly just above the thyroid. It lies on either side of the neck adjacent to the wall of the œsophagus, and external to the vascular and nervous trunks. In the healthy bird it varies considerably in size, and in three cases out of thirty-five controls it existed only in traces which were not weighable. Its variations in the male range between 100 mg. and 1,702 mg.; in the female between 85 and 776 mg. It varies in length from 1·1 to 5 cm., in breadth from 0·3 to 0·6 cm., and in thickness from 0·2 to 0·4 cm. The number of sausage-like swellings is also variable, usually being five or six. Its width at the point of junction of two 'sausages' is usually about 0·1 cm.

The gland is slightly more than twice as large in healthy males as in healthy females. The average weight in the former is 678 mg., in the latter 318 mg. Calculated per kg. of body-weight, the thymic tissue in male control birds amounts to 2·324 gm., in females to 1·201 gm.

In diseased birds the thymus atrophies out of all proportion to the body-weight. In males its average weight is reduced to 14 mg. The merest traces only (and these unweighable) could be found in thirteen of the diseased birds; in the remaining seven birds, in which a weighable thymus was dissected out, the weight of the organ ranged from 15 to 85 mg. In diseased females, on the other hand, the gland had completely disappeared in the present series, or existed only as a thin thread of tissue closely applied to the great vessels of the neck.

Funk has previously drawn attention to this atrophy of the thymus which is a very remarkable and constant feature.

The fact that it atrophies out of all proportion to the body-weight indicates, to my mind, that the organism, when deprived of certain substances essential for adequate metabolism, finds these for a time in the thymus and utilizes them to the point of complete exhaustion of the organ.

(v) OSSEOUS TISSUE

Thinning of the bones was constantly found to be present in diseased birds.

The bone marrow is reduced in amount in birds dying in consequence of this dietary.

(vi) THE TESTICLES

(a) *Anatomical Note*

In healthy and full-grown pigeons the testicles are very large organs. They lie on the surface of the kidneys, side by side, separated only one from the other by the main vesicular trunks and by the adrenal glands. In length they usually vary from 1·5 to 2·0 cm.; their breadth at the widest part may reach 1 cm., usually being 0·8 cm. They are oval in shape and round in section. The capsule is very thin and is covered with a very fine capillary network which is more marked on the external and lateral surface of the organ.

Perhaps one of the most remarkable results of a dietary deficient in so-called 'anti-neuritic vitamine' is the constant and very pronounced atrophy of the testicles in males and the similar but less pronounced atrophy of the ovary in females. The table (p. 99) gives the average weights of these organs in controls as 1·355 gm., in diseased birds as only 119 mg., or a reduction in size to about one-eleventh of their original volume, this proportion being maintained when the weight of the organs is calculated per kg. of body-weight.

I have examined histologically a number of testicles from diseased and healthy birds, and without going into minute details in this place it may be said that an exclusive dietary of milled rice causes after about thirty days a complete suppression of the function of spermatogenesis. The capsule of the gland with the inter-tubular trabeculae are greatly thickened; the number and the diameter of the tubules is much lessened; spermatozoa, spermatids and spermatocytes are wholly absent. The tubules are lined by a single, but incomplete, layer of cells which still preserve, in a considerable proportion of their numbers, nuclei which from their appearance seem capable of regeneration.

The most striking histological feature of the atrophic testicle is the change which occurs in the cell nuclei; and having regard to the fact that 'the nuclear matter conveys and determines or controls the inherited peculiarities' (Adami), it would be of great interest to observe, not only from the point of view of inheritance but also of variation and of sex determination, the offspring of animals deprived of 'vitaminic' substances to a point just short of suppression of spermatogenesis.

It is known that in cases of prolonged cachexia testicular atrophy may occur, but there is, I believe, no aetiological influence, apart from X-rays, hitherto known to us which is capable of causing such a degree of testicular atrophy as that of lack of 'vitamines'. It may be, indeed, that the testicular atrophy of prolonged cachexia and of tuberculosis is due to the lack, failure of assimilation or excessive waste of these essential substances. I think that in this remarkable result of 'vitaminic' deficiency we have a new aetiological fact in the genesis of reproductive inefficiency. Having regard to the stimulus to development and growth which the internal secretion of the gonads affords, the effects of 'vitaminic' starvation upon them are of the utmost importance to the growing child.

(vii) THE OVARY

(a) *Anatomical Note*

The ovary of the pigeon lies to the left of the middle line covering the upper half of the left kidney and having the left adrenal closely applied to its upper or renal surface. In control females its average weight is 253 mg., or 953 mg. per kg. of body-weight. In diseased females the average weight of the organ is 85·7 mg., or 305 mg. per kg. of body-weight.

In connection with the atrophy of the ovary it is important to recall the fact that beri-beric women cease to menstruate, the function only returning during convalescence (Vedder). They are, therefore, most unlikely to become pregnant. On the other hand, the pregnant woman is more apt than others to acquire the disease—a fact which is well understood since she has to supply her own 'vitaminic' needs as well as those of the foetus. Her child also is more likely to be born with congenital disorder of the adrenal glands and to suffer from wet beri-beri.

(b) '*War Amenorrhoea*'

The finding that lack of 'vitamines' in the food has a markedly deleterious effect on ovarian function is peculiarly interesting at the present time when so-called 'War Amenorrhoea' has become a matter of such importance for some of the belligerent nations. Many recent German periodicals refer to it with alarm, all authors commenting on its great increase in women of child-bearing age. They attribute it to defective nutrition under the existing food conditions, and to the fact that many women are now doing men's work. In the Charité-Frauenklinick in Berlin, according to Strickel,[1] cases of amenorrhoea are seven times more frequent than before the war. So grave is the outlook thought to be that Dr. Franziska Cordes,[2] a Berlin gynaecologist, fears it may lead to sterility and constitute a serious danger to the desired increase of population. Defective nutrition, underfeeding, anxiety or physical strain, cold and wet, enforced celibacy, are the possible causes which are advanced by German physicians to account for it. And in a general sense they are correct. My findings, however, indicate what is, I believe, the more essential cause—the lack in the food of certain accessory food factors requisite for the maintenance of sexual function.

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[1] Reported in *Brit. Med. J.*, ii, 734, 1917.

[2] Reported in *Lancet*, i, 712, 1918.

(viii) THE DIGESTIVE SYSTEM

In birds fed solely on milled rice the œsophagus is thin and often congested, the crop frequently empty. The stomach is greatly atrophied and may average as little as 3·514 gm., whereas in healthy pigeons its average weight is 5·716 gm. Its vessels are often found to be congested and its contents to consist of an emerald-green fluid which on culture has occasionally yielded *Bacillus pyocyaneus*. It may be taken, therefore, that one of the results of a dietary composed almost solely of starch is the tendency to growth in the stomach of organisms which are foreign to it; if these grow in the stomach they will grow also in the intestines.

The intestines are wholly devoid of fat and often greatly wasted. Their upper three or four inches, sometimes their whole length, are often much congested. When slit open and the mucous membrane examined under the lens, small ecchymoses are frequently seen. The walls are often greatly thinned and may be almost transparent, more rarely denuded in parts of epithelium. I have repeatedly cultured the duodenal contents, often aerobically, occasionally anaerobically, injecting the growth into healthy pigeons, but while such injections usually killed the birds and produced changes in the internal organs (especially thyroid, thymus, adrenals and testicles) of great interest, I have not observed in this series of birds that the injections produced symptoms comparable to beri-beri.

(a) *Intestinal Parasites*

The upper bowel is frequently full of tape-worms or round-worms; the latter, about one to two inches long, are very often found at autopsy to be quite dead, the former of the most extraordinary variety. In this respect, however, diseased birds are no different from healthy birds; the latter as frequently show the same parasites. The parasites do not appear to have favoured the onset of symptoms in these cases. It is to be noted, however, that in these experiments 'vitamines' were wholly lacking. One would expect to find that the influence, if any, of such parasites would come into operation only when there are in the food not enough 'vitamines' for both parasites and host. I do not, therefore, absolve them from all influence in determining the onset of symptoms under circumstances of minimal 'vitaminic' supply.

Even macroscopical examination of the lining of the small bowel, therefore, reveals the fact that its functional activity is greatly impaired.

It is thus seen that a diet too rich in starch and too poor in accessory food factors, as well as in other essential food constituents, not only impairs the functional activity of the gastro-intestinal tract, but permits of the growth therein of bacterial organisms in abnormal situations. A vicious circle is thus established which impairs the process of digestion at its very onset.

(ix) THE PANCREAS

(a) *Anatomical Note*

In pigeons the pancreas is a long, narrow, pale, coral-pink organ measuring 3–4 cm. in length and increasing gradually in breadth from 0·3 cm. at its upper pointed end to about 1·0 cm., or somewhat less, at its lower rounded extremity. It lies snugly in the narrow loop of intestine which forms the duodenum, the bowel being closely applied to its concave sides. It is divided longitudinally into two portions roughly triangular on section and joined together at their apices by areolar tissue. The average weight of the healthy male's pancreas is 0·95 gm., of the healthy female's 0·89 gm. The weight of pancreas tissue when calculated per kg. of body-weight is 3·254 gm. in males, 3·383 gm. in females. It is thus slightly larger in females than in males.

In diseased birds the organ is frequently of a dead-white colour, which may be universal throughout its entire length or confined to limited areas. It has rarely preserved the typical coral-pink appearance of health. Occasionally it is dark slate-grey in colour and ecchymoses or necrotic-like areas may be found on its surface. It is always much reduced in size. The average weight in males is 0·615 gm., in females 0·562 gm. As calculated per kg. of original body-weight, the pancreas tissue amounts to 2·082 gm. in males, to 2·004 gm. in females.

The pancreas is reduced in size to less than two-thirds of its original volume and weight. This loss of weight is not greatly out of proportion to the total loss of body-weight. Nevertheless, examination of the faeces affords evidence that the starch-splitting function of the organ is greatly impaired and the assimilation of carbohydrates much reduced.

Within fifteen to twenty days of the commencement of the experiment, partially or wholly undigested starch appears in the faeces, and as the experiment progresses the excreta may be composed almost wholly of undigested starch. This in itself may be sufficient to induce or to contribute to a state of acidosis, since the fact that certain intestinal bacteria are capable of attacking starches under anaerobic conditions, giving rise to acetic acid, aceto-acetic acid, propionic acid, butyric acid, acetone and succinic acid, appears to be well established. If this is so, it may be assumed that a condition of potential acid-intoxication is contributed to by acid-fermentation of starches in the bowel.

There is considerable clinical evidence pointing to the presence of such a state: the progressive change in the respirations, for example. It is a characteristic feature of the disease that the respirations diminish progressively in number while they increase greatly in depth, the gasping respirations of the bird nearing the end of life being highly suggestive of true 'air-hunger'. This characteristic hyperpnoea points to acid-excitation of the respiratory centre. In this connection it is interesting to compare the atrophy of the pancreas in inanition—in which acidosis is well known to occur—with that resulting from a milled-rice dietary.

(x) THE LIVER

(a) *Anatomical Note*

In healthy birds the average weight of the liver is 61·68 gm. in males, 5·405 gm. in females. As calculated per kg. of body-weight the liver tissue in males amounts to 21·136 gm., in females 20·371, being thus slightly greater in males. Wide variations in the weight of this organ are found to occur in pigeons of the same weight. Thus in the present series of nineteen control males it varied from 4·637 gm., in a bird weighing 275 gm., to 7·705 in another bird weighing 270 gm. In general, the weight of the organ is not proportionate to the body-weight of the bird. In control females this variation in the size of the apparently normal liver is not so great, ranging from 4·312 gm., in a bird of 260 gm., to 5·480 gm. in a bird of the same weight. The loss of weight of the liver in diseased birds is not proportionate to the general loss of body-weight.

In healthy birds the liver is of a uniform light chestnut colour often mottled with lighter areas. In diseased birds its macroscopical appearance varies considerably. In rare cases (four in thirty-four) it is of normal appearance but, as a rule, it is uniformly dark-chestnut in colour. It is frequently greatly congested and often diffluent, when it may be of a dark purple-red colour. Its vessels are often greatly engorged, especially in cases showing dilatation of the right heart, with or without hydropericardium. It is obvious that the state of passive hyperaemia so frequently present in the liver masks the true extent of its atrophy as determined by weight. Certain concurrent bacterial infections cause the organ to undergo great enlargement.

The macroscopical appearances of this organ are in themselves sufficient evidence of impairment of its function in a high proportion of cases. Biliary insufficiency may thus be regarded as contributing to a state of acidosis which may arise in consequence of intestinal fermentation and disordered carbohydrate metabolism.

(b) *General Effect of 'Vitaminic' Deficiency on the Digestive Organs*

The morbid anatomical evidence here brought forward indicates that gastric, intestinal, pancreatic and biliary disorders are amongst the most important of those disturbances induced by a dietary deficient in 'anti-neuritic vitamines'. It cannot, I think, be doubted that the depression of digestive function contributes to the symptom-complex.

There is much evidence pointing to defective assimilation and metabolism of carbohydrates which, when taken in conjunction with the pronounced respiratory changes, leads me to believe that a state of acidosis is undoubtedly present.

(xi) THE SPLEEN

A reference to the weight table (p. 94) will reveal the enormous degree of atrophy, amounting roughly to three-quarters of its former volume, which results in this organ in consequence of a diet of polished rice.

(a) *Anatomical Note*

The average weight of the spleen in healthy male pigeons is 339·2 mg., in females 284 mg. The organ is thus seen to be slightly larger in the male than in the female, but this difference is not so apparent when the weight of the organ is calculated per kg. of body-weight. The weight of spleen tissue in the control male is then found to be 1·162 gm., while in the control female it is 1·071 gm. In diseased birds its average weight in males is only 87·2 mg., and in females 71 mg. Per kg. of body-weight it is 295 mg. in the former, and 252 mg. in the latter.

The degree of atrophy is out of all proportion to the loss of body-weight. It may be assumed that the spleen—like the thymus, but in lesser degree—represents a store of body 'vitamines', as well as of other food materials, which are indented upon when these substances are absent from the food or not absorbed in amount sufficient for the needs of the body. It is thought that the chief organ which substitutes for the thymus is the spleen, and that it acts after the phase of involution of the former organ. In the morbid state resulting from this dietary, the thymus appears to atrophy with greater rapidity than does the spleen.

Such pronounced atrophy will greatly impair the haematopoietic and haematolytic functions of the organ. Its diminished output of trypsinogenin will also depress the proteolytic activity of the pancreas.

(xii) THE HEART

(a) *Anatomical Note*

The size of the pigeon's heart varies greatly in birds of approximately the same weight. In male control birds the weight of the heart has varied throughout the series from 2·395 gm. to 3·82 gm., the average being 3·084 gm. In healthy females this wide variation in size of the heart is even more considerable, the smallest heart in the series weighing 1·825 gm., the largest 3·985 gm., the average being 2·713 gm. When the weight of cardiac tissue is calculated per kg. of body-weight it is found to be 10·568 gm. in males and 10·228 gm. in females, or approximately the same in both sexes.

In diseased birds the same wide variations are found but on a lower level of weights; the weight of the smallest heart in the series of diseased males was 1·665 gm., of the largest 3·0 gm.; the average being 2·25 gm. In diseased females the smallest heart weighed 1·492 gm., the largest 3·5 gm.; the average weight being 2·139 gm. When the weight of the cardiac tissue is estimated per kg. of body-weight it is found to be 7·621 gm. in males and 7·621 in females, or the same in both sexes.

Cardiac atrophy is thus a conspicuous feature of the morbid states resulting from a diet of milled rice. This is all the more remarkable since hypertrophy of the heart is the rule in human beri-beri. Thus Ellis (1898) found the average weight of the heart, in 125 cases of beri-beri, to be 13·37 oz., while in 204 cases dying from other diseases the average weight was just under 9 oz.

Five features strike one in examining the hearts of these diseased birds: their small size as compared with those of healthy birds; the frequency of dilatation of the auricles and the right heart; the frequen lack of firmness of the heart's musculature; the degenerated appearance especially of the auricles; and the occasional presence of a band of oedema replacing the auriculo-ventricular band of fat. All these are not usually present in the same organ: as a rule its small size is the only conspicuous feature; the auricles dilated with clot being seated like a cap on the atrophic ventricles. It is not uncommon, in cases where hydropericardium is present, or where the right heart is much dilated, to find several of these features present together. Then on severing the heart from the great vessels and throwing it into a basin of saline it may be seen to collapse like an empty bag. Dilatation of the right heart has been almost constantly present with hydropericardium. There have however, been a sufficient number of exceptions to this rule to make the absence of dilatation a notable feature. Degenerative changes in the heart muscle are evidenced by the pale colour of its fibres, rarely throughout its whole extent, more usually in limited areas. The auricle walls are often very thin, sometimes even transparent in parts. One curious feature, which has been observed in many of these hearts, as well as in 50 per cent of cases dying of inanition, is oedema of the heart's musculature. This is usually confined to the area formerly occupied by the auriculo-ventricular band of fat. This band of oedema may extend round the heart at this point or be confined to limited areas. It is usually associated with great thinning of the auricle walls. In one remarkable case the whole musculature of the heart was oedematous, the surface of the organ being covered with a transparent layer of clear white-of-egg-like material, especially well marked at the auriculo-ventricular junction. Oedema of the heart is much more common in young and growing birds.

(b) *Hydropericardium*

Here reference may be made to the hydropericardium which was present in nine cases out of thirty-one, or in about 29 per cent in the first series (table, p. 101) and in 75 per cent in the second series of twenty cases (table, p. 104). In experiments conducted in 1914, when experimental beri-beri was produced in sixty-one pigeons as a result of the consumption of polished rice, my post-mortem notes record the presence of hydropericardium or oedema in 13·1 per cent of cases. These findings differ from that of Vedder and Clark who report that they 'did not find oedema or pericardial effusions in any of the fowls autopsied'. On the other hand, Shiga and Kasama found a great increase of pericardial fluid in some of their cases: 3 c.c. being present in the case of a dove and 10 c.c. in the case of one hen. It does not appear from the incomplete records of their work to which I have access that they noted the percentage of cases in which hydropericardium occurred. Eijkman similarly observed the occurrence of hydropericardium. There must be some important reason for these striking differences in the results of different observers.

The amount of fluid in the pericardial sac has varied in my series from a few drops to 13·5 c.c. I have included all cases in which a single large drop of fluid could be pipetted off from the pericardial sac, considering that these represent early stages in the process of effusion. Hydropericardium has been much more frequently met with in young and growing birds (table, p. 104).

In character the fluid is usually perfectly clear or amber-coloured without sign of turbidity, and sterile on bacteriological examination; in two cases only was the fluid blood-stained.

I have found no reason to believe that the oedema is primarily of cardiac origin, although a failing circulation ultimately contributes to it.

(xiii) THE VESSELS

Venous congestion is common, and at autopsy the great veins are often filled with clot. In one case the intravenous clotting extended to the femoral veins. No observations have been made with regard to the arteries.

(xiv) THE KIDNEYS

These organs have shown in the present series of cases only a slight degree of atrophy as estimated by weight. Macroscopically they appear to differ little in the majority of cases from those of healthy birds. In about 20 per cent of cases they are obviously congested.

(a) *Anatomical Note*

Great variations in size are observed in both healthy and diseased birds. There is no constant relationship between the size of the kidneys and the body-weight of the bird. In control males they have varied in weight from 1·222 gm. to 2·473 gm., the average weight being 1·594 gm. The weight of kidney tissue, as estimated per kg. of body-weight, was 5·464 gm. In control females these organs have varied in weight from 1·202 gm. to 1·925 gm., the average weight being 1·48 gm., or 5·578 gm. per kg. of body-weight.

In diseased birds the same wide variations are observed; the variations running in males from 1·371 gm. to 1·832 gm., the average weight being 1·563 gm., and the weight per kg. of original body-weight 5·298 gm. In diseased females the variations have ranged between 1·135 gm. and 2·445 gm., with an average of 1·543 gm., while the weight of kidney tissue per kg. of original body-weight is 5·55 gm.

The largest kidneys are usually those showing most evidence of congestion. There is, however, no uniformity in this regard between the kidneys and other abdominal organs, which would indicate that all are affected to the same extent by venous congestion. The largest kidneys are often found in birds with the largest adrenals, that is to say, in cases showing oedema in some form. There are, however, exceptions to this rule—large kidneys occurring with small adrenals and more rarely large adrenals with small kidneys. The relationship between the adrenals and kidneys in renal disease is still but little understood, but that some intimate connection exists is indicated by the hypertrophy of the adrenals which so constantly occurs in chronic Bright's disease. It is important, therefore, to consider what evidence these findings afford which would indicate that renal derangement is concerned in the causation of oedema.

Macroscopical observations afford no indications that the oedema is of renal origin. The rare occurrence of albuminuria in beri-beri is also against such a view. On the other hand, excess of adrenaline in the blood-stream inhibits, according to Gunning, the flow of urine. The diminished excretion of urine in beri-beri may therefore be connected with the adrenal hypertrophy which occurs.

(XV) THE THYROID APPARATUS

(a) *Anatomical Note*

The thyroids of the pigeon are small organs of the size and shape of a canary seed, lying below the root of the neck at its entrance to the thorax. They are situated under cover of the sternum about half an inch within the thoracic cavity and are extraordinarily rich in blood-supply. For this reason when removed from the body they appear somewhat smaller in size than when *in situ*. Enlargement of the organs is not uncommon in pigeons in northern India, but was absent from the series of thirty-five control birds from southern India which were employed in these experiments.

The average weight of both thyroids in healthy male pigeons is 24·7 mg., the variations in size ranging from 15 to 45 mg.; in female controls the average weight is 22·6 mg., the range of variation being 18 to 29 mg. As calculated per kg. of body-weight the thyroid tissue of control males weighs 84·7 mg.; of control females 85·5 mg., or approximately the same in both.

In diseased birds, on the other hand, males show a variation in weight of the organ of from 17 to 33 mg., with an average of 22·5 mg.; females a variation of from 13 to 30 mg., with an average of 21·2 mg. The weight of thyroid tissue per kg. of body-weight is 76 mg. in males and 75·8 mg. in females, or approximately the same in both sexes. In arriving at these figures I have excluded one case in which the thyroids were greatly enlarged, weighing 133 mg. As this was the only case in the series of sixty-nine birds in which goitre was present, it was considered to be attributable to causes other than the dietetic deficiency.

The slight degree of atrophy of the thyroids has been for me one of the surprises of these experiments. It amounts to about one-tenth part of the weight of the organs when calculated against the original weights of the birds: a degree of atrophy which is considerably less than that resulting from simple inanition. Previous work led me to comment on this atrophy of the thyroid, first observed by Funk, but I did not—nor, so far as I can ascertain, did he—weigh the organs in each case against an equal number of controls. Nor did I then realize that some of the histological changes I observed were the result of septicaemic states plus food deficiency.

I have not yet examined a sufficient number of thyroids histologically to enable me to arrive at a definite conclusion as to the extent of the depression of their function in consequence of a polished-rice dietary. The histological study of the sixty-nine pairs of thyroids removed in these experiments will form the subject of a subsequent paper.[1]

(xvi) THE ENDOCRINE GLANDS IN GENERAL

Lack of ‘vitamines’, when associated with a diet too rich in starch, is thus seen to lead to disordered function of the whole endocrine system. This disturbance of function is due in part to nuclear starvation of the organs which compose this system, in part to failure of their efficient sympathetic control, and in part to disturbances of their correlations. Disordered endocrine function leads in its turn to imperfect carbohydrate assimilation, to marked disturbances of carbohydrate metabolism, and amongst other things to resultant atrophy of muscular tissue which is such a conspicuous feature in these cases. (For histopathology of spleen, liver, pancreas, kidneys, pituitary and thyroid, see Nos. 25 and 71 in Bibliography.)

THE CENTRAL NERVOUS SYSTEM

(xvii) BRAIN

(a) *Anatomical Note*

In male control pigeons the weight of the brain ranges between 1·767 gm. and 2·84 gm., the average being 2·01 gm. In female controls it ranges between 1·642 gm. and 1·990 gm., the average being 1·861 gm. When calculated per kg. of body-weight, the weight of brain tissue is approximately the same in both sexes, being 6·91 gm. in males and 7·015 gm. in females.

In diseased birds the same variations are observed, the range in males being 1·811 gm. to 2·95 gm., with an average of 1·986 gm.; and in females 1·515 gm. to 1·94 gm., with an average of 1·862 gm. As calculated per kg. of original body-weight, the brain tissue amounts to 6·84 gm. in males and 6·635 gm. in females.

A slight degree of atrophy of the brain is thus seen to result from the dietetic deficiency; it will be observed in contrast that no atrophy of the brain occurs in simple inanition.

The macroscopical appearances of the organ and its membranes are by no means constant. Hyperaemia of the meninges is occasionally seen, more rarely the hyperaemia also affects the brain substance. On the other hand, the brain and its membranes may present quite norma appearances, or the brain substance may be of a peculiar whiteness similar to that so constantly seen in inanition, and indicative of pronounced anaemia. Perhaps the most frequent evidence of disease is softening. This increased diffluence has been observed in a considerable proportion of cases. I was unable to find from macroscopical examination alone any constant gross anatomical appearances peculiar to those cases in which brain symptoms were marked. Anaemia and softening have been as frequent features as hyperaemia.

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[1] Number 24 in Bibliography.

Points of difference in symptomatology between experimentally-produced beri-beri in birds and the disease as it occurs in man are the great frequency of brain symptoms and convulsive seizures, and the pronounced inco-ordination in the avian form of the malady. These points have been investigated by Richter, who found changes indicative of progressive degeneration of the nerve cells; the areas most affected were groups of cells in the corpus bigeminum (optic lobe) on both sides, the large cells being swollen and vacuolated. He came to the conclusion that in pigeons the clinical picture is that of a severe disturbance of the centre of gravity, due to marked disturbance of function of groups of cells within the sphere of the cerebellum, a conclusion with which I am in agreement.

(xviii) THE CORD

Macroscopically the cord in the majority of cases appears to differ little from that of healthy birds. Occasionally, it seems to be thinner than usual and to have retracted from the walls of its bony canal. I have observed no accumulation of fluid in the spinal canal. A few cords have been examined microscopically after treatment by Marchi's method; in these degenerated fibres have been found here and there throughout the section and in the nerve roots.

THE NERVES

Both sciatics and one or both vagi have been examined for diagnostic purposes in all cases in the present series of sixty-nine birds. The nerves were treated by Marchi's method and examined in teased preparations. The nerves of each case were all treated alike; the same specimen tube being used for all four. The results observed were as follows:

(xix) THE SCIATICS

(a) *Controls*

Typical Wallerian degeneration was present in 33·3 per cent of healthy pigeons, none of which exhibited any signs of nervous disease. These changes were due to causes other than dietetic deficiency since the birds received a very liberal dietary of mixed grains including *mung dal* and sand. In view of this result it is obvious that degenerative changes in the sciatic nerves of pigeons do not constitute a safe basis on which to estimate the effects of a peculiar dietary on the nervous tissues.

(b) *Diseased Birds*

Degenerative changes were present in one or other or both sciatic nerves in thirty out of thirty-four diseased birds, or 88 per cent. These changes ranged from irregularity of outline and diffuse staining of the medullary sheath to completely atrophic tubules empty of degenerated myelin or containing it only in isolated droplets. These later stages of the degenerative process were most frequently observed in birds which survived the dietary for the longest period.

It is remarkable how slight may be the evidence of degenerative change, as demonstrable by Marchi's method, in the sciatics of diseased birds. In some cases, not more than three or four fibres throughout the whole thickness of the nerve could be definitely stated to be diseased. Very rarely about one fibre in five was found to be degenerated. Vedder's estimate of a maximum of 10 to 15 per cent of diseased fibres has, generally speaking, been my experience. In two cases, however, this estimate was greatly exceeded.

It is evident from the comparative frequency with which degenerative changes may be found in the sciatic nerves of pigeons in robust health, and from the fact that certain cases of the experimentally produced disease in pigeons are so readily and so rapidly curable by the administration of 'vitamine'-containing solutions that the extent of the nerve degenerations in these birds is rarely sufficient to cause permanent paralysis. The paralytic symptoms are mainly functional in character, due to impairment of function of nerve cells. Total loss of function of nerve cells is the exception, not the rule. No clinical experience is more remarkable than that which is afforded by the case of a bird one day exhibiting in pronounced degree symptoms of the cerebellar type of the disease with frequent convulsive seizures, in which it turns 'cart-wheels' backwards, great inco-ordination and astasia, and the next, after treatment, say, with the alcoholic extract of the yolks of four eggs, capable of flying about the laboratory and of alighting with comparative ease on the edge of a table or other convenient perch. Residual paralysis in such cases is often hardly noticeable. Clearly no extensive amount of permanent damage to the cells of the central nervous system could have occurred when such rapid recovery is possible.

(xx) THE VAGI

I have found degenerative changes usually of a patchy type in the vagus of nineteen cases out of thirty examined. Very occasionally these changes were observed in one nerve only; frequently they were of slight degree and in three cases only were fibres seen exhibiting the typical Wallerian appearances.

Similar changes have been found in the vagi of control pigeons in six cases: in one of these a single fibre showing typical Wallerian degeneration was found.

In view of the comprehensive and authoritative work of other observers—notably Richter, Vedder and Clark—on the histology of the central nervous system both in experimental beri-beri and in the disease as it occurs in man it has seemed to me unnecessary to repeat it. Enough cases have been examined to convince me of the accuracy of the view they have enunciated that the paralytic symptoms observed in both avian and in human beri-beri are the result not of a neuritis but of disturbance in function of the cells of the brain and cord. As a rule, degenerative changes in these nerves are not so advanced as to preclude recovery on the substitution of an efficient dietary or on the administration of 'vitaminic' substances in suitable doses. In about 4 to 15 per cent of nerve cells, however, the degeneration is complete and death of their axones results, the extent of recovery possible and the amount of residual paralysis being dependent on the extent of permanent damage to nerve cells. These changes in the central nervous system are in conformity with those which take place in other organs and tissues of the body: they are no greater nor are they more important. The fact that their symptomatic manifestations are so readily recognizable has caused undue prominence to be given to them, with the result that no less important pathological processes in other organs have been largely overlooked.

(xxi) THE SYMPATHETIC SYSTEM

My examination of sympathetic nerve tissue has so far been confined solely to the ganglia frequently to be found intimately attached to the adrenals in pigeons. The staining methods employed were not such as are specially adapted to nerve-cell histology. Nevertheless, the contrast afforded in normal and in diseased birds leaves little room for doubt but that degenerative changes do occur in the nerve cells of these ganglia.

The histology of the sympathetic system in human beri-beri has been fully studied by Ellis, so long ago as 1898. Thus, in man, Ellis 'examined a large number of nerves removed from patients dying of beri-beri, and met with many cases in which all the peripheral nerves were healthy, but in which some or all of the following nerves were markedly degenerated, viz. phrenic branches of the cardiac and pulmonary plexuses, the splanchnics, branches of the solar and renal plexuses, branches to the mesentery and vasomotor branches to the aorta, renal, splenic and tibial arteries. In no case of death from beri-beri have I failed to find degeneration of either the phrenic, pneumogastric or branches from the cardiac plexuses, showing it seems to me definitely that death invariably occurs in the disease from implication of some of these nerves.'[1]

III. INFECTION AND DEFICIENCY DISEASE

The experimental evidence which I have to advance in this connection relates in the main to certain results observed in the year 1914.

A preliminary account of these appeared in this Journal in 1914.[2]

Briefly summarized, the results were these:

(1) The presence of *Bacillus suipestifer* in the birds used in these experiments was fortuitous but none the less instructive.

(2) Birds fed on polished rice and so infected developed symptoms of polyneuritis more rapidly than non-infected birds.

(3) Asthenic and fulminatory forms of polyneuritis were much more frequent in infected birds.

(4) The infection could be stayed by isolation and immunization. Under these circumstances birds almost invariably developed the cerebellar type of the disease.

(5) The most important finding is the comparative immunity enjoyed by control birds fed on a liberal diet of mixed grains although exposed to infection. Appropriate food is thus shown to afford protection against the invasion of the body by—or the growth therein of—certain highly virulent organisms. A diet deficient in accessory food factors, on the other hand, renders the body highly susceptible to such invasion and greatly favours the rank growth of bacteria in the blood and tissues: such a diet facilitates the invasion of the body by organisms which may themselves be capable of causing polyneuritis.

(6) Hydropericardium was present in 13 per cent of cases of polyneuritis in this series: it was not present in cases of polyneuritis resulting from the inoculation of *B. suipestifer* into pigeons fed on mixed grains. Oedema was more common in isolated and immunized pigeons (20 per cent) than in those infected with *B. suipestifer* (8·3 per cent).

(7) In infected birds, the liver was almost constantly noted to have

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[1] Quoted from Vedder's *Beri-beri*.

[2] Number 86 in Bibliography.

been greatly enlarged and hyperaemic and frequently the spleen also. The intestines were often much congested. The thyroid varied as to size and degree of congestion. The adrenals were not examined; the importance of these organs in the genesis of symptoms not then being realized.

(8) The reproductive organs and thymus were constantly noted to have been greatly atrophied in infected cases as well as in those cases developing in segregated or immunized birds.

(9) Atrophy of the reproductive organs and thymus, hyperaemia of the thyroids and kidneys, congestion of the intestines, and great enlargement with hyperaemia of the liver were the main post-mortem findings noted in pigeons developing polyneuritis as a result of the subcutaneous inoculation of *B. suipestifer* into birds receiving a liberal diet of mixed grains. In a considerable number of these cases the symptoms of polyneuritis were present for a week or more prior to the bird's death.

Atrophy of the reproductive organs and thymus is thus liable to occur under the metabolic stress of septicaemic invasion.

In cases of polyneuritis, with concurrent septicaemia autopsied during the present year (1918), the average weight of the liver was 7·78 gm., being well above the average of health. *Bacillus suipestifer* has not been encountered in cases of polyneuritis autopsied during the present year. The following organisms have been met with: (1) *B. pyocyaneus*, which is known to exert a highly deleterious action on the adrenal glands; (2) an organism not yet identified, which kills pigeons on subcutaneous injection within twenty-four hours, causing haemorrhages into the tissues including the heart's muscle, skeletal muscles and intestines; post-mortem appearances highly suggestive of scurvy. This organism causes great enlargement of the adrenal glands. In three cases in which it was isolated the adrenals weighed 95, 105 and 110 mg. respectively. When these were injected in emulsified form into the circulation of sheep, kymographic tracings of the arterial blood-pressure showed only slight rises amounting to 14, 24 and 14 mm. of mercury respectively. The enlargement of the adrenals in these cases was not accompanied with any corresponding increase of their adrenaline content.

These experiences are held to afford an instructive illustration of the influence which infectious agencies may reasonably be expected to exert in man under like conditions of dietetic deficiency. It is recognized that such agencies are not a necessary factor in the genesis of beri-beri, but their influence in favouring the onset of symptoms, and probably in determining the endemicity or epidemic-like spread of the disease in the human subject, cannot be ignored.

IV. GENERAL CONCLUSIONS

(1) The absence of certain accessory food factors from the dietary—improperly termed 'anti-neuritic'—leads not only to functional and degenerative changes in the central nervous system but to similar changes in every organ and tissue of the body. The morbid state to which their absence gives rise is not a neuritis.

(2) The symptom-complex resulting from the absence of these substances is due: (a) to inanition, (b) to derangement of function of the organs of digestion and assimilation, (c) to disordered endocrine function, especially of the adrenal glands, and (d) to malnutrition of the nervous system.

(3) Certain organs undergo hypertrophy; others atrophy. Those which hypertrophy are the adrenals. Those which atrophy, and in the order of severity named, are the thymus, the testicles, the spleen, the ovary, the pancreas, the heart, the liver, the kidneys, the stomach, the thyroid and the brain.

The pituitary gland showed a slight tendency to enlargement in adult male pigeons only.

(4) The enlargement of the adrenals is a true hypertrophy; it is associated with a proportionate increase of the gland's adrenaline content. The amount of adrenaline in the hypertrophied organ is, area for area, approximately the same as that found in the adrenals in health. The hypertrophy is equally well marked in both sexes.

(5) Oedema has invariably (100 per cent) been associated with great hypertrophy of the adrenal glands: 86 per cent of all cases having great hypertrophy of these organs had oedema in some form. The amount of adrenaline, as determined by physiological methods, in such cases has been considerably in excess of that found in cases not presenting this symptom, and greatly in excess of that found in normal adrenals.

(6) Inanition gives rise to a similar state of adrenal hypertrophy; and to a similar state of atrophy of other organs—the brain excepted.

(7) The oedema of inanition and of (avian) beri-beri is believed to be initiated by the increased intracapillary pressure which results from the increased production of adrenaline, acting in association with malnutrition of the tissues. Failure of the circulation and venous stasis may subsequently contribute to it. Age is an important factor determining its occurrence.

(8) Wet beri-beri and dry beri-beri are essentially the same disease; the former differs from the latter in the greater derangement of the adrenal glands.

(9) Gastric, intestinal, biliary and pancreatic disorders are important

consequences of a dietary too rich in starch and too poor in 'vitamines' and other essential constituents of the food. It is suggested that some of the obscure metabolic disorders of childhood might be examined from this viewpoint.

(10) A state of acidosis results from the absence of so-called 'anti-neuritic vitamines'; this state is due to the imperfect metabolism of carbohydrates and to acid-fermentation of starches in the intestinal tract. Clinically, it is evidenced in pigeons by progressive slowing and deepening of the respirations.

(11) Great atrophy of muscular tissue results from deficiency of 'anti-neuritic vitamines'.

(12) Profound atrophy of the reproductive organs is an important consequence of 'vitaminic' deficiency. It leads to the cessation of the function of spermatogenesis. In the human subject such degrees of atrophy would result in sterility in males and in amenorrhoea and sterility in females. This finding is held to account in great measure for the occurrence of 'War Amenorrhoea'.

(13) The central nervous system atrophies little: the paralytic symptoms are due mainly to impaired functional activity of nerve cells; much more rarely to their degeneration.

(14) It is thought that, because of their atrophy out of all proportion to other tissues, the thymus, the testicles, the ovary and the spleen provide a reserve of accessory food factors for use on occasions of metabolic stress. This reserve, however, is rapidly exhausted.

(15) The bones are thinned and there is a loss of bone-marrow.

(16) The red cells of the blood are diminished by about 25 per cent.

(17) The whole morbid process is believed to be the result of nuclear starvation of all tissue cells. Even the adrenals, which alone of all organs of the body undergo hypertrophy, show on section changes in some of their cells indicative of nuclear starvation.

(18) Finally, although deficiency of certain accessory food factors is the essential aetiological factor in the genesis of beri-beri, it is held that infectious and parasitic agencies may often be important causes determining the onset of symptoms.

(19) 'Vitaminic' deficiency renders the body very liable to be overrun by the rank growth of bacteria.

'Anti-Neuritic Vitamines'

Throughout the course of this paper, I have employed the commonly accepted terminology as applied to those accessory food factors the lack of which is the essential cause of beri-beri—'anti-neuritic vitamines'.

It will be recognized, I think, from the morbid anatomical evidence I have brought forward that the adjective is inaccurate and the noun inapt. The morbid state resulting from the lack of these substances is not confined to the nervous system, nor is it a neuritis; the term 'anti-neuritic' is, therefore, inaccurate. It is not proven that these accessory food factors are of the chemical nature of amines nor that they contain nitrogen; the term 'vitamine' is thus inapt. To the uninitiated its derivation is obscure and its meaning uncertain. The main sources of these substances in the food are the germs of vegetable seeds and the eggs of animals. They are said to be constituents of nucleic acids. They are certainly nuclear ingredients essential for the nutriment of the living nucleus. They are 'nuclear nourishers' without which multiplication of cells does not occur. The term nucleopast (that which feeds the nucleus) might well be applied to them.

The Effects of Deprivation of 'B' Accessory Food Factors[1]

In a previous report the clinical and morbid-anatomical effects of an exclusive dietary of autoclaved rice were recorded.[2] Such a dietary is lacking in all three classes of accessory food factors, is deficient in proteins and fats, and has an excess of starch.

In the present paper I have to record the clinical and morbid-anatomical effects of a dietary of autoclaved rice to which butter and onions were added. This dietary contained an abundance of 'A' and 'C' accessory food factors but was deficient in the water-soluble 'B' factor as well as in proteins, and had an excess of starch.

The observations were made on pigeons exhibiting no evidences of concurrent disease, whose blood was sterile at the time of death.

Since butter is not a normal constituent of the food of pigeons it was necessary to control the observations by adding it to the natural food of healthy birds.

I. THE EFFECTS ON HEALTHY PIGEONS OF A DIETARY TOO RICH IN FATS

Twenty-four pigeons were fed on a liberal diet of mixed grains to which chopped onions and butter (to the extent of one-twelfth of an ounce per bird) were added. For a contrast, twenty-four healthy pigeons were fed on a diet of mixed grains only. In the latter there was a slight and gradual increase in the average weight, in the former the weight curve rose acutely up to the end of the fourth week, when it began to decline.

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[1] Extract from number 68 in Bibliography.

[2] Number 67 in Bibliography.

In the table below the average weights of the organs per kg. of body-weight in twenty-four pigeons fed on mixed grains, butter and onions are contrasted with those of thirty-five pigeons fed on mixed grains only.

Average weight per kg. of body-weight in (1) twenty-four pigeons fed on mixed grains, butter and onions; (2) twenty pigeons fed on autoclaved rice, butter and onions; (3) thirty-five pigeons fed on mixed grains only; and (4) thirty-one pigeons fed exclusively on autoclaved rice.

Organs	(1) *Controls with Butter and Onions*	(2) *Beri-beri, Autoclaved Rice with Butter and Onions*	(3) *Controls without Butter and Onions*	(4) *Beri-beri, Autoclaved Rice without Butter and Onions*
Thyroids	88·3 mg.	69·7 mg.	85·1 mg.	75·9 mg.
Liver	26·107 gm.	19·388 gm.	20·703 gm.	18·666 gm.
Spleen	1·480 ,,	0·225 ,,	1·116 ,,	0·273 ,,
Heart	11·033 ,,	7·148 ,,	10·398 ,,	7·621 ,,
Kidneys	5·728 ,,	5·471 ,,	5·521 ,,	5·399 ,,
Adrenals	69·7 mg.	161 mg.	95·1 mg.	144·2 mg.
Thymus	1·752 gm.	Trace only	1·762 gm.	0·023 gm.
Testicles	4·853 ,,	0·279 ,,	4·643 ,,	0·401 ,,
Ovary	1·215 ,,	0·356 gm.	0·953 ,,	0·305 ,,
Pancreas	3·806 ,,	2·084 ,,	3·318 ,,	2·043 ,,
Brain	6·262 ,,	7·212 ,,	6·962 ,,	6·739 ,,
Pituitary	17·3 mg.	18·5 mg.	20·2 mg.	21·0 mg.
Stomach	20·345 gm.	16·819 gm.	—	—
Lungs	8·808 ,,	9·782 ,,	—	—
Average weight of birds	308 ,,	276 ,,	280 gm.	288 gm.

NOTE. The weights of the organs of diseased birds (columns 2 and 4) are calculated against the original body-weights of the birds.

A reference to columns 1 and 3 of this table reveals the fact that the addition of butter and onions to the dietary of healthy pigeons causes marked differences in the weights of their organs as compared with those of birds fed on the more natural dietary of mixed grains. These differences may be regarded as departures from normal and in some sense as evidences of morbidity. It will be observed that the organs group themselves into three classes:

(1) Those showing no appreciable difference in weight: the thymus.

(2) Those showing a difference in weight in the direction of increase: the spleen, the ovary, the liver, the pancreas, the stomach, the heart, the testicles, the thyroid, the kidneys; the degree of increase being in the order in which the organs are named.

(3) Those showing a difference in weight in the direction of decrease: the adrenals, the brain and the pituitary.

It may, I think, be assumed that these differences are in the main due to the addition of butter to the dietary of mixed grains, rather than to the addition of onions. If this be so, it may be concluded that the overloading of the body with fats leads to changes in the digestive and vascular systems which, it may be presumed, will ultimately cause a relative impairment of their functional capacity.

The most notable finding in this experiment is the smaller size of both the adrenals and the pituitary in healthy birds to whose dietary the unnatural food—butter—was added. It is to be noted that these two glands are the only organs in the body (with the exception of the brain) so affected. It will be seen also that under conditions of vitaminic deficiency these glands are the only organs of the body (again with the exception of the brain) to undergo enlargement. These findings indicate that the adrenals, the pituitary and the brain are very sensitive to food influences and that such influences affect their weight in like manner.

II. THE EFFECTS OF A DIETARY OF AUTOCLAVED RICE, BUTTER AND ONIONS

The dietary employed in these observations consisted of milled rice, autoclaved at a temperature of 130° C. for three-quarters of an hour, butter—to the extent of one-twelfth of an ounce per bird—and finely chopped onions. There was a dual object in adding the onions: to provide an abundance of 'C' accessory food factor and at the same time a natural antiseptic. Of this mixture the birds ate greedily: the average daily consumption being between 30 and 40 gm. per bird.

1. *Clinical Observations*

The birds developed avian beri-beri—often of the cerebellar type—with marked rapidity. The first case occurred after twenty-days' consumption of the autoclaved rice-butter-onion mixture, the last—of twenty—on the thirty-sixth day. Several cases showed no symptoms other than pronounced asthenia, while three escaped all evidences of disease for fifty days.

The symptomatic manifestations of disease resulting from this dietary were similar to those previously described as resulting from an exclusive diet of autoclaved rice; convulsive seizures were, as a rule, less marked. They call for no further reference. The loss of body-weight was rapid.

More detailed observations with regard to the respiratory rate and the body-temperature were made in this series. Both the respiratory rate and the body-temperature begin to fall within the first week of the experiment. To my mind there is little doubt but that the depression of respiratory rate, associated as it is with a deepening of the respirations, is the effect of acid-irritation on the respiratory centre.

2. *Morbid Anatomical Observations*

The general appearances of these birds after death was similar to that found in birds fed exclusively on autoclaved rice. The average loss of body-weight during the same period of time (forty-three days) was slightly different in the two series: in the one the average loss was 86 gm., in the other 94 gm.

The most characteristic post-mortem feature in these birds was their comparative freedom from evidences of oedema. This circumstance will be dealt with in detail in a subsequent paper.

The table (p. 125) gives the average weight of the organs in these birds per kg. of body-weight as compared with the fat-fed controls.

It will be observed from this table that the organs group themselves into three classes:

(1) Those which remain unchanged: the pituitary.

This result controls and substantiates that observed in pigeons fed exclusively on autoclaved rice; it leaves little room for doubt but that the pituitary is not involved in the generalized atrophy of the body-tissues resulting from the deficient dietaries.

(2) Those which undergo enlargement: the adrenals, the lungs and the brain.

It is a remarkable fact that the pituitary, the adrenals and the brain should show an increase in size under the conditions of the present experiment, whereas they are the only organs which are smaller than normal when the unnatural food—butter—is added to the normal food of healthy pigeons.

(3) Those which undergo atrophy: the thymus, the testicles, the spleen, the ovary, the pancreas, the heart, the liver, the thyroids, the stomach, the kidneys; the degree of atrophy being in the order in which the organs are named.

To these must be added the intestines which undergo pronounced atrophic changes, especially marked in the upper three or four inches which embrace the pancreas.

III. CONCLUSIONS

(1) The morbid state which results in pigeons from deprivation of accessory food factors of the 'B' class resembles closely that resulting from complete vitaminic starvation (deprivation of all three classes of vitamines A, B and C), but is much less often associated with oedema.

(2) There appears to exist in unmilled rice, as well as in butter or onions, or both, some factor which tends to prevent the onset of oedema.

(3) Two food factors appear to be concerned in the production of avian beri-beri: (a) the so-called anti-neuritis factor, and (b) an anti-oedema factor.

The Influence of Dietaries Deficient in Accessory Food Factors on the Intestine[1]

I. INTRODUCTION

The pathological changes in the intestine which result from dietaries deficient in accessory food factors have been studied in:

(1) pigeons fed exclusively on autoclaved milled rice: that is to say, on food lacking in all three classes of accessory food factors;
(2) pigeons fed on autoclaved rice together with fresh butter and onions: that is to say, on food deficient in accessory food factors of the 'B' class;
(3) pigeons fed on autoclaved rice together with fresh butter: that is to say, on food deficient in accessory food factors of the 'C' class (anti-scorbutic substances), as well as in factors of the 'B' class (the so-called 'anti-neuritic vitamines');
(4) guinea-pigs fed on a diet of crushed oats and autoclaved milk: that is to say, on food deficient in anti-scorbutic substances; and
(5) guinea-pigs fed on an exclusive diet of autoclaved rice: that is to say, on food deficient in all three classes of accessory food factors.

While the morbid changes resulting from these dietaries are attributable in the main to deficiency of accessory food factors, their genesis is no doubt contributed to, or their effects enhanced, by deficiency of other essential attributes of a satisfactorily balanced ration.

All experiments were carried out under conditions and precautions previously detailed:[1] they were continued to a point at which death of the animals occurred or was about to occur.

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[1] Extract from number 69 in Bibliography.

II. THE EFFECTS OF AN AUTOCLAVED RICE DIETARY ON THE INTESTINE OF PIGEONS

The pathological changes were studied macroscopically in 152 pigeons fed exclusively on milled or on autoclaved milled rice, and microscopically in 24. All these birds developed polyneuritis in consequence of the deficient dietary.

1. *Macroscopical Appearances*

The chief macroscopical features observed at autopsy in the intestine were atrophy and congestion, both of which might be extreme. All cases presented atrophy in greater or lesser degree, while a proportion, estimated at about 30 per cent, showed no congestion appreciable by the naked eye.

The upper portion of the intestine of healthy pigeons, especially that part embracing the pancreas, is thick and muscular. It is this portion which suffers most in consequence of the deficient dietary. The atrophy is of all grades of severity; it may be comparatively slight, or progress to a point at which the intestinal walls are so thin as to be transparent. As a rule the atrophy is more marked the longer the bird is under the influence of the defective diet.

The congestion is commonly confined to the upper part of the alimentary tract; less often it involves its whole extent. The branches of the mesenteric vessels surrounding the bowel may be greatly engorged, and extravasations of blood are occasionally to be seen under its serous coat.

On splitting open the bowel, the upper three to six inches are often found to be distended with tape-worms, more rarely with round-worms—the latter usually dead, the former almost invariably alive. Round-worms have occasionally been found in the œsophagus.

On examining the surface of the bowel with the hand lens, varying degrees of atrophy and erosion of the mucous membrane are encountered. These are not always uniformly distributed over the whole surface of the bowel; some areas show them in greater degree than others. Ecchymoses are common over the mucous surface; in the more severe cases pin-point haemorrhages into the bowel lumen are to be seen.

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[1] Number 67 in Bibliography.

2. *Histo-Pathology*

Apart from some degree of atrophy of all coats of the bowel, which is universal in birds dying in consequence of this dietary, no marked histological changes, with the exception, it may be, of slight congestion, are found in approximately 30 per cent of cases. In the remainder the histo-pathological appearances are very striking, although widely variable in degree in different birds.

The pathological changes comprised the following:

(i) congestion and haemorrhage;
(ii) atrophy of the myenteron;
(iii) degenerative changes in the myenteric plexus of Auerbach;
(iv) atrophic and inflammatory changes in the mucous membrane;
(v) atrophy of lymphoid structures;
(vi) fibrosis; and
(vii) changes favouring systemic infection from the diseased bowel.

(i) CONGESTION AND HAEMORRHAGE

In its mildest form, this change consists in engorgement of the subperitoneal vessels, and in distension of the small vessels ramifying between the muscularis mucosae and the base of the crypts of Lieberkuhn, or the glandular structures corresponding to these in birds. The process of congestion is not usually limited to distension of vessels in these areas, but may extend to those of the villi. The next stage in the congestive process is the occurrence of actual haemorrhages around the bases of the crypts. In some cases an almost continuous layer of haemorrhage may surround the bowel at this point. Such remnants of villi as remain are often seen to be much engorged or to contain effusions of blood: this appearance is frequently very pronounced in the lower bowel Free corpuscles may occasionally be found in the lumen of the bowel or exuding from its congested and frayed mucous membrane.

A further, or simultaneous, state in the process is the spread of these haemorrhagic areas from the submucous coat into the myenteron: these may involve only the circular layer of muscle fibres or penetrate to the longitudinal layer. It is not unusual to see large tracts of the circular layer of muscle broken up by extensive haemorrhages into its substance. Such haemorrhages cause separation and rupture of the muscle fibres. The ruptured fibres may present ragged edges enclosing the collection of effused blood or the haemorrhages may be more diffuse, the corpuscles being scattered throughout the whole thickness of the myenteron and penetrating to the serous coat.

Added to these appearances is the engorgement—often intense—of the vessels running under the serous coat and ramifying in the muscular layers. Oblique and longitudinal sections of these vessels may at first sight present the appearance of haemorrhagic effusions. Rupture of the vessel walls is, however, rare.

One can often see an uninterrupted stream of blood corpuscles extending from an engorged and atrophic villus—the epithelial covering of which is incomplete—directly into the large subperitoneal vessels.

Oedematous infiltration of the coats of the bowel has occasionally been encountered.

Intense congestion of, and haemorrhages into, the coats of the bowel —and especially into the coats of the upper bowel—sometimes leading to actual breaches in their continuity, are, therefore, amongst the results of a dietary deficient in all classes of accessory food factors. It may be assumed that resolution of such haemorrhages would lead to the deposition of fibrous tissues in the myenteron and serous coat.

(ii) ATROPHY OF THE MYENTERON

The average thickness of the circular layer of the muscular coat, at a point one to two inches from the stomach. It is not of the same thickness at every point of the bowel's circumference, but gradually merges from a thickness of about 0·35 mm. to one of about 0·25 mm.

In pigeons fed on the deficient diet the degree of atrophy of the circular muscular layer varies considerably. The muscular coat is usually thinnest in birds which survive longest, or in which infection of the bowel walls has occurred; it is atrophied, as a rule, to the extent of one-half to one-quarter its normal thickness in health and its efficiency is thus proportionately reduced. Added to this are frequent haemorrhages, the rupture and separation of muscle fibres thereby, and, less commonly, segmentation and fragmentation of these fibres. The extent to which the motor function of the bowel may be impaired by the deficient dietary will be realized from these statements.

(iii) DEGENERATIVE CHANGES IN THE MYENTERIC PLEXUS OF AUERBACH

Careful scrutiny is necessary in order to detect, in healthy birds, the ganglionic swellings of this plexus, as they lie between the circular and longitudinal layers of the myenteron. They are compact bodies of oval form varying considerably in size, the variations being of course dependent on their point of section. They fit snugly between the layers of muscle and give rise to little or no bulging in the contour of these layers.

In haematoxylin-stained sections of the intestine from birds fed on the deficient dietary these ganglia are much more obvious and catch the eye at once. Their readier recognition may be due in part to the fact that the atrophy and recession of the circular and longitudinal muscle fibres renders them more prominent. Their greater prominence is, however, often the result of swelling, due probably to oedematous infiltration. In size they vary within wide limits, dependent in some measure on their point of section. In general, they are double or treble the size of healthy ganglia. The cytoplasm of the ganglionic cells may appear shrunken, their nuclei more excentric than normal, and the nucleoli almost invariably fragmented, the last appearance being the most constant. Occasionally, whole cells or groups of cells appear to have disappeared, leaving in the ganglion lacunae empty of cellular structure.

There can, I think, be little doubt that the plexus myentericus is involved in a degenerative process. This being so, it may be concluded that the nervous control of the bowel is impaired in proportion to the degree of degenerative change.

(iv) ATROPHIC AND INFLAMMATORY CHANGES IN THE MUCOUS MEMBRANE

These consist in: (a) atrophy and partial or complete disappearance of the villi; (b) frequent congestion of such villi as remain; (c) atrophy of the glandular cells of the crypts of Lieberkuhn, and separation of these from their basement membrane; (d) partial or complete disappearance of the lymphoid cells lying between and around the crypts; (e) thinning, or actual disappearance in places, of the muscularis mucosae; (f) a relatively greater proportion of reticular cells, and the scattered deposition of fibroblasts; (g) an increased proportion of leucocytes in the atrophic mucous membrane, and, more rarely, (h) bacterial invasion with intense inflammatory and necrotic changes in the mucous membrane and underlying coats of the bowel.

These appearances are most marked in birds which have survived the dietary for the longest time, or in which infections of the bowel wall are found at autopsy. They are rarely present in the same degree at every area of the bowel's circumference. Sections of even the most severely affected intestines may show some areas in which these changes are much less marked than in others.

(v) ATROPHY OF LYMPHOID STRUCTURES

In the healthy pigeon the lymphoid cells fill in the spaces between the crypts, and present a continuous layer of varying thickness between the bowel lumen and the muscularis mucosae. In diseased birds this protective layer is atrophied in greater or lesser degree. In some areas it was completely wanting; and the muscularis mucosae also had frequently disappeared.

(vi) FIBROSIS

The evidences of fibrosis are scanty in so far as the mucous membrane itself is concerned. The loss of lymphoid cells and the atrophy of the secretory elements bring into greater prominence the fibrous reticulum. Areas, however, are encountered in which there is a deposition of scattered fibroblasts.

(vii) INFECTION FROM THE DISEASED BOWEL

Systemic infection is rendered more easy in the presence of these pathological processes owing: (a) to impaired production of digestive juices; (b) to continued congestion of the mucous membrane and consequent malnutrition of its secretory cells; (c) to loss of the protective layer of lymphoid cells; (d) to increased leucocytic invasion of the mucous membrane and to increased leucocytic traffic in micro-organisms between the bowel mucous membrane and the blood-stream; (e) to the greater facilities which the debilitated mucous membrane provides for the growth of bacteria on its surface and in its substance; (f) to the imperfect digestion of food in the upper alimentary tract, which affords a favourable medium for the growth of micro-organisms; and, although more rarely, (g) to actual breaches of continuity in the walls of the bowel itself. Occasional specimens have shown a direct continuity of blood corpuscles from an eroded villus to the blood-vessels running external to the serous coat.

Cases are encountered with comparative frequency in which the atrophic and congestive processes had superadded to them the effects of intense bacterial invasion of the bowel walls. In such cases bacteria of various types were to be found in large numbers throughout the necrotic mucous membrane and lying also in the submucous and muscular coats. By special staining methods bacteria (chiefly cocci) have been detected in the vessels of the submucosa, and bacteria-laden leucocytes are common objects in the microscpoic field. In these circumstances, bacterial organisms may pass directly into the blood-stream from the infected bowel walls. In four such cases I cultured from the heart's blood at autopsy, by aerobic methods, a small coccus in two, a coliform organism in a third, and bipolar organism in a fourth. Infection of the blood from the bowel is therefore no uncommon consequence of 'vitaminic' deficiency.

In connection with these lesions in the upper alimentary tract of pigeons fed exclusively on autoclaved milled rice it is to be remembered that Hamilton Wright[1] was so impressed with the constancy of pathological changes in this situation in human beri-beri that he attributed this malady to a specific gastro-duodenitis. As is is now well known, the pathological changes he described are not the cause of beri-beri; they are, however, important evidences of deficiency of certain accessory food factors in the diet. The fact that Hamilton Wright found a bacillus of constant morphological character in this situation is important. Although the organism is not the specific cause of beri-beri, its presence is an illustration of the fact that the wall of the upper intestine may become infected in the human subject in consequence of such a dietary.

III. THE EFFECTS OF A DIETARY OF AUTOCLAVED RICE, BUTTER AND ONIONS ON THE INTESTINE OF PIGEONS

A dietary of autoclaved rice, butter and onions, while it is deficient in accessory food factors of the water-soluble 'B' class, contains an abundance of anti-scorbutic substances and of accessory food factors of the fat-soluble, or 'A' class. Forty-two pigeons were fed on this dietary: all developed polyneuritis. The birds were noted to have eaten greedily of the chopped onions—sparingly of the rice. The fresh onions used must have contained but a scanty supply of accessory food factors of the 'B' class, since the onset of polyneuritis was not prevented thereby although considerably delayed.[2]

The macroscopical evidences of pathological change in the intestines of pigeons so fed were studied in forty-two cases. The microscopical changes were studied in serial sections of the upper, middle and lower bowel in twelve cases.

It was noted that naked-eye evidences of congestion, haemorrhage and other pathological processes were less frequently encountered in pigeons whose basal diet of autoclaved rice was enriched with fresh butter and fresh onions; notable evidences of congestion were slight or nil in 50 per cent of all cases.

The atrophy of the bowel, although often considerable, was usually less marked than in cases dying in consequence of complete 'vitaminic' starvation. Histologically one did not, as a rule, encounter the same degree of congestion: actual haemorrhages were more rarely met with, while the degree of atrophy of the myenteron and of the elements of the mucous membrane, although usually considerable, were often comparatively slight. Two cases were encountered amongst twelve examined where bacterial infection of the bowel walls had assisted in bringing about changes as pronounced as those so commonly seen in the case of birds wholly deprived of accessory food factors.

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[1] Hamilton Wright. Quoted from Vedder's *Beri-beri* (London, 1913).

[2] Number 68 in Bibliography.

Fresh butter and onions when added to a dietary of autoclaved rice thus provide some at least of those factors on which the functional perfection of the alimentary tract is dependent.

IV. THE EFFECTS OF A DIETARY OF AUTOCLAVED RICE AND BUTTER ON THE INTESTINE OF PIGEONS

The effects of this dietary, which is deficient in 'vitamines' of the 'B' and 'C' classes and gives rise to typical polyneuritis, were studied macroscopically in eighteen cases and microscopically in six.

The description given of the effects of complete 'vitaminic' starvation applies to these cases. The butter used afforded the birds no protection in so far as the intestines were concerned.

With the reservation that the number of birds in this category is small in comparison with those in the two previous categories, one is led to suspect that, since butter did not protect, it was the addition of fresh onions to the basal diet of autoclaved rice that afforded the birds in the second category the measure of protection against congestive and haemorrhagic processes which they undoubtedly enjoyed.

In order to provide further evidence on this point, the appearances presented by the intestines of guinea-pigs fed on dietaries, (a) of crushed oats and autoclaved milk, and (b) of autoclaved rice, were studied.

V. THE EFFECTS OF A SCORBUTIC DIET ON THE INTESTINE OF GUINEA-PIGS

Twelve guinea-pigs, with an equal number of controls, were employed in this experiment. The animals were isolated in separate cages. They were fed on crushed oats and autoclaved milk. The oats were locally grown and were of poor quality. The milk was autoclaved at a temperature of 130° C. for one hour. The experiment was continued to the death of the pigs, which occurred within periods ranging from twenty to thirty days. Autopsies were performed immediately after death with the detail and precautions previously described.[1] Three of twelve guinea-pigs were excluded owing to the presence of complicating pathological processes, such as peritonitis. The macroscopical appearances found in the gastro-intestinal tract were studied in nine cases; the microscopical in five.

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[1] Number 67 in Bibliography.

1. *Macroscopical Appearances*

The most notable feature present was intense congestion of the duodenum. This part of the bowel, for a variable distance from the pylorus, was, in four out of nine cases, so congested as almost to present the appearances seen in strangulated bowel. The congested area was sharply demarcated by the pylorus and extended down the bowel for a distance of from one to two inches. In two other cases the congestion of the duodenum was of a patchy character. In the three remaining cases moderate congestion of the whole bowel was present in two, while no appreciable congestion was present in the third.

In contradistinction to the appearances presented by the upper intestine of pigeons, where the bowel is often greatly thinned, the duodenum of guinea-pigs was usually swollen and turgid, the tumefaction being due largely to haemorrhagic infiltration of all coats of the bowel.

On opening the duodenum and examining the mucous surface with the hand lens, ecchymoses were frequently to be seen, while areas resembling punched-out ulcers, whose base extended almost to the peritoneal coat, were occasionally encountered. At these areas the bowel walls were almost transparent.

The intestinal tract is thin in healthy guinea-pigs. Apart from the duodenum, the bowel walls in pigs dying in consequence of the deficient dietary were, generally speaking, thinner than in health. In three cases of the nine referred to, punched-out necrotic ulcers were found in the stomach. In one case as many as fifteen were counted, the base of the ulcer extending down to the peritoneal coat, the mucous membrane of the stomach being studded with the brownish debris of haemorrhages into the interior of the organ. Thus localized, destructive changes in the mucus and underlying coats of the stomach and duodenum are amongst the more occasional results in guinea-pigs of a dietary of crushed oats and autoclaved milk.

These changes were present in the gastro-intestinal tract of guinea-pigs, dying in consequence of this dietary, which exhibited none of the characteristic naked-eye appearances of scurvy. In a clinical sense, then, they may be regarded as pre-scorbutic.

2. *Histo-Pathology*

The microscopical appearances seen in sections of the duodenum in these cases comprised:

(i) turgidity, with diffuse haemorrhagic infiltration of all coats of the bowel;
(ii) degenerative changes in the myenteron;
(iii) degenerative changes in the myenteric plexus; and
(iv) atrophic and necrotic changes in the cellular elements of the mucous membrane.

These lesions resemble closely those described in the case of pigeons fed on an exclusive dietary of autoclaved rice. In general the same description applies to both. In the case of guinea-pigs the more diffuse haemorrhagic infiltration of the mucous membrane may impart to it a degree of turgidity which is not seen in pigeon. The degenerated process involves the ganglia of the myenteric plexus in a manner similar to that described in pigeons. In some cases, more especially in the vicinity of extensive haemorrhagic infiltration of the myenteron, the normal histological structure of the ganglia may be much altered. In these circumstances, ganglia may be encountered which are infiltrated with blood, and in which no single cell contains a normal nucleus. As in the case of diseased pigeons so also in guinea-pigs, the myenteric plexus is much more prominent than in health. In haematoxylin-stained sections the ganglia appear swollen, the nerve cells ill-defined, the nuclei degenerated and the nucleolus fragmented. Not all cells, however, are so affected in either species, some exhibiting nuclei of apparently normal structure. Without definitely asserting that the degenerative changes in the myenteric plexus are more pronounced in guinea-pigs than in pigeons, they certainly appear to be no less. There can be little doubt that neural lesions, which may impair the nervous control of the bowel, result in consequence of this dietary; further histological study by special methods is necessary to determine their character.

The myenteron also is often, although not always, greatly disorganized in consequence of diffuse haemorrhagic infiltration of its substance; in such circumstances separation of muscular fibres with their segmentation and fragmentation are common appearances. The degenerative and necrotic changes in the mucous membrane are as pronounced in guinea-pigs as in pigeons, and are of similar character. The same comments as to the facilities which these pathological processes afford for infection of the bowel walls and for systemic infection therefrom, apply with equal force to both species.

The histological changes in the lower bowel are of like character to those found in the upper bowel, but more moderate in degree.

VI. THE EFFECTS OF AN AUTOCLAVED RICE DIETARY ON THE INTESTINE OF GUINEA-PIGS

For the purpose of this study four guinea-pigs were employed. They were fed on an exclusive diet of autoclaved rice until death occurred, which event took place within forty-six days of the initiation of the experiment.

My post-mortem notes with regard to the intestinal tract in these animals read as follows:

No. 1. The duodenum shows intense congestion, the first inch and a half looks almost gangrenous, so intense is the congestive process; there is a well-marked ulcer at one point, its base extending to the peritoneal coat, so that only the serous covering appears to intervene between the bowel lumen and the abdominal cavity. Both small and large bowel are congested, while they appear thinner than in health.

No. 2. Perhaps the most interesting pathological appearance is that presented by the duodenum. This part of the bowel is much congested, its vessels being greatly engorged; two haemorrhagic areas of extensive proportions almost surround the bowel circumference. On opening the duodenum, congestion of the mucous membrane was seen to be pronounced and numerous ecchymoses were scattered over its surface; the viscus was transparent at one part, the peritoneal coat alone appearing to intervene at this area between the bowel lumen and the abdominal cavity.

No. 3. The doudenum is much congested and turgid and its mucous membrane is studded with capillary haemorrhages. The rest of the bowel is excessively thin.

No. 4. Apart from a moderate degree of generalized congestion of the bowels, and abnormal tenuity, no noteworthy macroscopical characters were recorded.

It appears, then, that congestive, haemorrhagic, atrophic and necrotic changes in the bowel walls, usually most pronounced in the upper intestine, are common consequences in guinea-pigs of dietaries deficient in accessory food factors. It will have been noted that in both pigeons and in guinea-pigs, the pathological processes are similar in character as well as in distribution. The relatively less-frequent presence of these lesions in pigeons whose dietary was deficient in the 'B' factor only, the fact that pigeons deprived of both 'B' and 'C' factors suffered from pathological lesions of the bowel as pronounced as did those deprived of all three classes of accessory food factors, the fact that these lesions were equally well marked in guinea-pigs subjected to complete 'vitaminic' starvation and in guinea-pigs deprived only of the 'C' factor, indicate that the congestive and haemorrhagic lesions in the intestines of both species are largely, if not mainly, due to the absence of fresh green vegetable foods from the dietary. Control guinea-pigs fed on crushed oats, autoclaved milk and on abundance of fresh vegetables were wholly protected from gastro-intestinal lesions.

Having regard to the readiness with which accessory food factors of the 'C' class are destroyed in the process of cooking, their absence from the dietaries of human beings, or their long-continued subminimal supply, may have an important bearing on the genesis of gastro-intestinal disorders. These observations appear to provide an explanation of the beneficial action of orange juice on the digestive and assimilative processes in bottle-fed infants.

Before leaving this subject, I would again direct attention to the fact that the intestinal lesions I have described in guinea-pigs were present in the majority of my cases before clinical evidences of scurvy were apparent. I suggest, therefore, that the symptoms of scurvy, as described in text-books, are the gross evidences of a disordered state of metabolism, the minor or pre-scorbutic manifestations of which are probably frequently overlooked, especially in children.

VII. COMMENTARY

Interpreted in terms of bowel function, the derangements to which such pathological changes as have been described may ultimately lead can be grouped as follows:

(1) Impairment of the neuro-muscular control of the bowel; impaired transport of the intestinal contents along the alimentary canal.

(2) Impairment of assimilative power.

(3) Impairment of secretory function.

(4) Impaired protective resources leading to infection of the mucous membrane of the bowel by pathogenic saprophites or ingested bacteria, and to systemic infection therefrom.

Unwilling as I am to apply too directly to the human subject the experimental results of intensive 'vitaminic' starvation as observed in birds and in guinea-pigs, we may, I think, regard the changes I have described as applicable in some degree to man.

It is my experience that, while complete deprivation of accessory food factors will cause the relatively rapid appearance of so-called 'polyneuritis' in birds, subminimal provision of these substances, protracted over-prolonged periods of time, will, especially in young and growing birds, eventually lead to a like morbid state. It is, I think, with sustained subminimal supply of accessory food factors that the physician is mainly concerned in practice. Complete 'vitaminic' deprivation is, as I have pointed out in another place, relatively rare; incomplete 'vitaminic' deprivation—or subminimal supply of accessory food factors—is relatively frequent. If, in the light of the histo-pathological findings here recorded, we consider the case of children fed, it may be from birth, on foods deficient in these essential substances, and the frequency with which in later life their dietary continues to be ill-balanced and defective, we are, I venture to think, in a position to realize the ultimate consequences of such a dietary and to anticipate the sequence of events leading up to grave derangements of bowel function. Food deficiency also prepares the soil for bacterial growth and the resultant morbid states will vary with the nature of the organisms which may become implanted upon it. This knowledge, if it does not enable us to account fully for such gastro-intestinal disorders as mucous disease, coeliac disease, and chronic intestinal stasis, will at least help us to a better understanding of their genesis.

1. *Mucous Disease*

I have referred to the fact that pigeons fed on an exclusive dietary of autoclaved rice frequently suffer from diarrhoea,[1] and have pointed out that this symptom of 'vitaminic' deficiency can, in a proportion of cases, be made to disappear, often with surprising rapidity, by the administration of the alcoholic extracts of the yolks of eggs. Others have drawn attention to the almost constant occurrence of diarrhoea or of colitis as precursors or concomitants of the condition known as 'war oedema', a malady proved to be due to food deficiency.[2] Clinical evidence of bowel derangements due to this cause are, therefore, not lacking. If, then, we attempt, from the results of our histo-pathological observations, to provide an explanation of the origin of mucous disease, we may, I think, surmise that continued subminimal 'vitaminic' supply will lead to that state of chronic gastro-intestinal catarrh which characterizes this disorder.

Mucous disease is very common amongst European children in India who are fed largely on sterilized milk (milk, which, in my own experience, is often poor in 'vitaminic' content), artificial foods, white bread, polished rice, poor butter, over-cooked vegetables and excessive quantities of sugar. Therapeutic experience of this malady shows how readily it yields to limitation of carbohydrates and to a rationally balanced dietary of good 'vitaminic' quality. The mucous stools, the diarrhoea, the peevishness, the unhealthy appetite rapidly disappear on such a regimen, as also do the 'night terrors' from which the subjects of mucous disease so frequently suffer.

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[1] Number 67 in Bibliography.

[2] Park, F. S., *J. Amer. med. Ass.*, 70, 1826–7, 1918.

I do not wish to dogmatize with regard to the genesis of this malady. I would but draw attention to the fact that an ill-balanced diet, deficient in accessory food factors, is capable of giving rise in pigeons to a state of chronic congestion of the intestinal mucosa, often accompanied with hypertrophy of the adrenal glands; the relief afforded to children suffering from mucous disease by the correction of their ill-balanced dietaries may find an explanation in this fact.

2. *Coeliac Disease*

One cannot read the illuminating account of this disorder given by Dr. G. F. Still[1] in his recent Lumleian lectures without considering the possibility that it also may owe its origin to similar dietetic deficiencies. Its absence in breast-fed children, its onset between the age of nine months and two years, the diarrhoea which so frequently precedes it, the cessation of growth, the ill-formed pale 'oatmeal' stools, the frequent association of scorbutic symptoms, the abdominal distension, the afebrile nature of the malady, the diminished size of the liver, the blood changes, the occurrence of oedema, the thin bones, the muscular feebleness—all these find their counterpart in pigeons fed on an exclusive dietary of autoclaved milled rice.[2] The pathological findings recorded in this paper indicate with what readiness pathogenic organisms may invade the atrophying intestinal mucous membrane and lead to inflammatory states and fibrotic thickenings therein. The enlargement of the adrenals, which is so constant a result of 'vitaminic' starvation, and so frequently associated with oedema in birds, may not be wanting in coeliac disease; I can find, in the literature available to me, no records with regard to the adrenals in this malady.

I venture to suggest that those who have the opportunity should examine their cases of coeliac disease, and more especially all available post-mortem material, from the point of view of food deficiency. Whether or not this malady is found to be due primarily to such deficiency, it would appear probable that a number of its characteristics are secondary to the imperfect assimilation of these essential ingredients of the food.

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[1] Still, G. F., *Lancet*, ii, 163–6, 193–7, 227–9, 1918.

[2] Number 67 in Bibliography.

If, now, we consider the possibility of subminimal 'vitaminic' supply protracted over prolonged periods from childhood onwards, we have, I think, a new view-point from which to consider the genesis of that common disorder:

3. *Chronic Intestinal Stasis*

In the recent edition of Sir Arbuthnot Lane's work on this subject,[1] Professor Arthur Keith draws attention to two anatomical factors which he regards as of primary importance in the causation of chronic intestinal stasis: (1) defective action on the part of the abdominal musculature, and (2) a lesion of the neuro-muscular system of the intestine.

The histo-pathological findings recorded in this paper indicate one means by which both the abdominal musculature and the neuro-muscular system of the intestine may be simultaneously impaired in functional capacity. Deficiency of certain accessory food factors leads to atrophy of all muscular tissue as well as to disordered function or actual degeneration of motor nerve cells throughout the entire body. The abdominal musculature and the nerve elements controlling it must of necessity suffer along with other muscular and nervous tissues. It may be concluded, then, that defective action on the part of the abdominal musculature will ultimately result in consequence of deficiency of accessory food factors.

In addition to this functional defect on the part of the abdominal wall, we find also in pigeons and in guinea-pigs starved of 'vitamines' unquestionable evidence in the wall of the intestine itself of neuro-muscular lesions of great significance. Whether or not we are justified in applying these findings to the genesis of stasis in the human subject, we may at least regard with suspicion human food which does not conform to standard in respect to perfect 'vitaminic' balance.

There can be no doubt that the dietaries of children amongst the poorer, and often amongst the richer, classes are frequently deficient in these important ingredients. Subsistence on such ill-balanced dietaries from childhood onwards may be regarded as calculated to lead to defect of the abdominal musculature, to neuro-muscular lesions of the intestine and to changes in the glandular elements of its mucous membrane. Indeed, the pathological changes in the large bowel in stasis, as described by Professor Keith, are strikingly similar to those I have enumerated as occurring in pigeons fed on a 'vitamine'-free food. He describes the morbid changes as affecting two systems—the glandular and the neuro-muscular: 'The chief change in the muscular coats of the diseased great bowels removed from cases of enterostasis is a fibrosis—one which mainly affects the tissue between the outer and inner coats of the bowel, the intermediate stratum which insheathes the myenteric plexus. Degeneration in areas of the musculature, particularly of the outer longitudinal coat, also occurs. In every case there are inflammatory changes varying in degree. There are many marked changes in the lining glandular epithelium and in the submucous coat. One notes also that there is engorgement of the subperitoneal vessels, and that the subperitoneal tissue is much thicker and denser than is normal.' Having regard to the fact that the pathological processes I have described are acute in nature, and induced by intensive 'vitaminic' deprivation, whereas those recorded by Professor Keith are chronic, the similarity between them suggests that subminimal 'vitaminic' supply protracted from an early age has a fundamental influence in causing the lesions found in stasis. However this may be, we must regard with suspicion an influence which is capable of providing at once the anatomical conditions necessary for the development of stasis and the facilities for systemic infections which are known to result from it.

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[1] Lane, Sir W. Arbuthnot, *The Operative Treatment of Chronic Intestinal Stasis*, 4th edition (London, 1918).

Observations on the Effects of 'Vitaminic' Substances as Curative Agents in 'Polyneuritis Columbarum'

In the course of the present research, many observations have been made with regard to the curative action of 'vitaminic' extracts, and also of such whole grains as *mung dal* in the morbid state induced in pigeons by an exclusive dietary of autoclaved rice. Since these therapeutic trials bring into prominence certain points of interest, the following illustration may be given:

Two young pigeons developed polyneuritis in typical form and in severe degree as a result of an exclusive diet of autoclaved rice and butter. Both birds presented pronounced cerebellar symptoms and astasia; both had severe convulsive seizures turning 'cart-wheels' backwards at frequent intervals.[1] At this stage, the birds were artificially fed with the dry whole grains of *mung dal* (a species of pea). Within twenty-four hours the convulsions had ceased, the cerebellar symptoms had disappeared, and both birds were able to walk, although with a high-stepping and uncertain gait. They improved hourly on this dietary, both eating greedily of it. After the lapse of seventy-two hours one died suddenly. An autopsy was performed immediately; the whole gastro-intestinal tract was greatly engorged, the bowel walls were very thin and the upper four or five inches of the bowel distended with partly-digested grain, the lower bowel being practically empty. It was noted that the contents of the upper bowel were not of that creamy consistency which is usual in health, but resembled rather a coarsely-ground collection of the ingested grain. The transport of the intestinal contents along the bowel lumen was delayed. Histological examination revealed pronounced changes in the bowel walls. The heart's blood yielded no growth by aerobic methods of culture.

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[1] Number 67 in Bibliography.

The other bird survived. It was placed subsequently on mixed grains, and with the exception of a high-stepping and somewhat unsteady gait, it exhibited after four days no symptoms referable to the nervous system. It appeared to be perfectly restored in health within ten days.

In connection with this illustration I would direct attention to the following facts:

(i) The nervous symptoms present in *polyneuritis columbarum* may be rapidly ameliorated, or even recovered from, and yet the bird die in consequence of gastro-intestinal lesions or (as I have found in other cases) of haemic infections.

(ii) The rapid recovery from nervous symptoms indicates that the nervous system is, of all others, the least affected as regards organic lesions. In this system the symptoms are mainly the result of functional disorder. In the intestine, on the other hand, a greater destruction of tissue cells takes place. The intestinal lesions will consequently be recovered from more slowly.

(iii) Solutions of 'vitaminic' substances (such, for example, as a solution in water of the dried alcoholic extract of the yolks of eggs) will, when administered to birds suffering from avian beri-beri, often cause recovery to take place with extraordinary rapidity. In cases, such as are recorded in the above illustration, recovery from nervous symptoms was quickly brought about by artificial feeding with the small Indian pea known as *mung dal*. The question then arises as to whether the liberation of accessory food factors from the dry hard seeds of *mung dal*, in quantity sufficient to bring about so rapid an amelioration of nervous symptoms, is wholly due to the ordered processes of digestion. It is hardly credible that a gastro-intestinal tract, in which are present the grave pathological changes I have described, could complete the processes of digestion with sufficient despatch to secure so rapidly beneficial a result. Indeed, in the bird which died, digestion was far from complete, the bowel contents were abnormally delayed in transit and histological examination revealed an extreme degree of pathological change in the bowel walls. One is led to surmise, therefore, that some process more rapid than that of digestion may be concerned in the liberation of these substances—a process comparable, it may be, to the generation of growth ferments in seeds planted in warm, moist earth.

VIII. CONCLUSIONS

(1) Dietaries deficient in accessory food factors give rise in pigeons and in guinea-pigs to congestive and atrophic changes in all coats of the bowel, to lesions of its neuro-muscular mechanism, to impairment of its digestive and assimilative functions, and to failure of its protective resources against infection.

(2) The functional perfection of the gastro-intestinal tract is dependent in considerable measure on the adequate provision of accessory food factors derived from fresh fruit and vegetables.

(3) Certain gastro-intestinal disorders in the human subject—of which three examples are referred to—may owe their origin to the long-continued subminimal supply of accessory food factors.

The Influence of a Scorbutic Diet on the Adrenal Glands[1]

The influence of a scorbutic diet of crushed oats and autoclaved milk on the adrenal glands was studied in guinea-pigs.

The animals were isolated in separate cages. The experiment was continued until death occurred. Autopsies were performed with the attention to detail previously described.[2] Aerobic cultures of the heart's blood at autopsy gave negative results in four cases, positive results in one (No. 5, of table, p. 146). In this case the organism isolated failed to kill guinea-pigs on subcutaneous injection in large dosage.

I. MORBID ANATOMY

Increase in size of the adrenal glands together with greater or lesser degrees of congestion were the main naked-eye changes observed. The yellow colour of the organs was usually found to have given place to a reddish-yellow tinge. The superficial vessels presented varying degrees of engorgement. Minute haemorrhagic effusions under the serous coat were frequently encountered.

The weight of the adrenals of guinea-pigs dying in consequence of the scorbutic diet was approximately double that of health (see table, p. 146). Whereas the gross weight of both organs in healthy guinea-pigs ranged between 0·390 and 0·520 gm., with an average weight of 0·467 gm., in

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[1] Extract from number 70 in Bibliography.

[2] Number 67 in Bibliography.

The adrenaline content of the adrenal glands, the total adrenaline per kg. of body-weight, etc., in (a) five guinea-pigs fed on a scorbutic diet, and (b) in four healthy guinea-pigs fed on normal food

No. of Guinea-pig	*Original Weight of Guinea-pig (gm.)*	*Final Weight of Guinea-pig (gm.)*	*Weight of Adrenals (gm.)*	*Weight of Adrenals per kg. of Original Body-weight (gm.)*	*Weight of Adrenals per kg. of Final Body-weight (gm.)*	*Total Adrenaline in both Adrenal Glands (gm.)*	*Total Adrenaline per kg. of Original Body-weight (gm.)*	*Total Adrenaline per kg. of Final Body-weight (gm.)*	*Total Adrenaline per gm. of Gland*	*Experimental or Control Animal*
1	2	3	4	5	6	7	8	9	10	11
1	550	390	0·850	1·545	2·179	0·000113	0·000205	0·000289	0·000132	Experimental
2	520	400	1·029	1·978	2·572	0·000143	0·000275	0·000357	0·000139	,,
3	500	320	0·850	1·700	2·656	0·000096	0·000192	0·000300	0·000112	,,
4	550	320	0·900	1·636	2·812	0·000116	0·000210	0·000362	0·000128	,,
5	520	390	1·150	2·211	2·948	0·000086	0·000165	0·000220	0·000074	,,
	528	364	0·955	1·814	2·633	0·000110	0·000209	0·000305	0·000117	Averages
7	570	620	0·390	0·684	0·629	0·000253	0·000443	0·000408	0·000648	Control
8	610	610	0·520	0·852	0·852	0·000216	0·000354	0·000354	0·000415	,,
9	610	610	0·460	0·754	0·754	0·000253	0·000414	0·000414	0·000550	,,
10	670	670	0·500	0·746	0·746	0·000233	0·000347	0·000347	0·000466	,,
	615	627	0·467	0·759	0·745	0·000238	0·000389	0·000380	0·000519	Averages

NOTE. I am indebted to Colonel Cornwall, I.M.S., for the figures relating to guinea-pigs Nos. 8, 9 and 10. Owing to difficulty in obtaining supplies of pure anhydrous phosphoric acid and of sodium-tungstate, I was unable to estimate the adrenaline content of the adrenal glands in my controls to this experiment (with the exception of pig No. 7). The figures given for cases Nos. 8, 9 and 10 are the results of estimations made by Colonel Cornwall for another purpose in three healthy guinea-pigs from laboratory guinea-pigs fed on the scorbutic dietary, the weight of both glands ranged between 0·850 and 1·150 gm., with an average weight of 0·955 gm. The increase in weight due to the scorbutic diet was even more marked when the weight of the glands was calculated per kg. of original and of final body-weight.

II. ADRENALINE CONTENT OF THE ENLARGED GLANDS

The adrenaline content was estimated by the method of Folin, Cannon and Dennis.[1] In each case one gland was used for adrenaline estimation, the other for histological study. On the presumption that both organs were affected in like degree, the total adrenaline content of both adrenals was calculated from the results obtained with one gland. In some instances the right gland was used for adrenaline estimation, in others the left. The results of these estimations are shown in the table (p. 146).

Analysis of Table

(1) The total quantity of adrenaline in both glands in guinea-pigs fed on a scorbutic diet was less than half that present in healthy guinea-pigs (table, p. 146, col. 7), although the weight of the organs was more than twice as great in the former as in the latter. (Table, p. 146, cols. 4, 5, 6.)

(2) Similarly, the total adrenaline per kg. of original body-weight (i.e. the weight of the animal before the experiment commenced) was little more than half that of health (table, p. 146, col. 8.)

(3) When calculated against the final body-weight (table, p. 146, col. 9) of the guinea-pig, the total adrenaline per kg. was found to be less markedly reduced; that is to say, the total adrenaline production does not diminish in proportion to the diminution of body-weight.

(4) The total adrenaline per gm. of gland was less than one-fourth of that found in health. (Table, p. 146, col. 10.)

(5) It will be noted that in guinea-pig No. 5, in which a coliform organism was cultured from the heart's blood at autopsy, the adrenaline content was considerably less than in the other four animals in which no infection was detected by aerobic methods of culture.

A pronounced reduction n the amount of adrenaline in the adrenal glands was thus found to result in guinea-pigs from a scorbutic dietary of crushed oats and autoclaved milk.

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[1] Folin, O., Cannon, W. B. and Dennis, W., *J. biol. Chem.*, 13, 477, 1912–13.

In connection with these findings it is of interest to direct attention to the fact that the total adrenaline per gm. of gland in healthy pigeons is ten times greater (0·0023 gm.) than in healthy guinea-pigs (0·00023 gm.). This greater proportion of adrenaline in birds may bear some relationship to the fact that they excrete uric acid as such. The work of Bauer,[1] which leads him to believe that 'the function of the adrenal cortex is the making of pigment from the superfluous uric acid in the blood', is of interest in this connection. He considers that the pigment, which he believes to be made by the cortex, is transformed by the medulla into adrenaline.

A further point of interest in connection with these findings is the contrast they afford to the great increase in the adrenaline content of the adrenal glands which occurs in pigeons wholly deprived of accessory food factors of all classes. In another place,[2] I have shown that the adrenaline content of the organs in these birds is largely dependent on the class of accessory food factor which is absent from their dietary.

III. HISTO-PATHOLOGY

The histological changes in the adrenal glands which result from a scorbutic dietary comprise:

(1) Haemorrhagic infiltration, and

(2) degenerative changes in the cellular elements of the medulla and cortex.

1. *Haemorrhagic Infiltration*

There are two features of importance in connection with the haemorrhagic infiltrations:

(i) Their circumscribed character and situation in the adrenal cortex; and

(ii) the fact that they may occur before any clinical evidences of scurvy are observed, and even before any notable scorbutic changes are to be found at autopsy between cartilage and rib.

The haemorrhagic infiltration is not confined to engorgement of the capillary spaces of the cortex but results in more or less circumscribed haemorrhages into scattered areas of the cortex. These haemorhagic areas are of varying size; their more or less uniform distribution around the periphery of the cortex is their characteristic feature. I have not observed this curious distribution of haemorrhages in the adrenal glands of guinea-pigs dying of infectious diseases in which both cortex and medulla are often extensively congested. The haemorrhagic areas were distributed more or less uniformly around the periphery of the cortex in three cases in the present series. They were present on only one side of the adrenal cortex in one case. In the fifth case they were absent, a moderate degree of generalized haemorrhagic infiltration of the cortex alone being present.

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[1] Bauer, —., *Virchow's Arch.*, 225, 1, 1918.

[2] Number 87 in Bibliography.

The changes in the cortical cells consist in (a) loss of their tessellated appearance, (b) vacuolation and disintegration of cells, and (c) disappearance or loss of staining reactions of their nuclei. These changes are well seen in the photomicrographs which illustrate the original paper (No 70 in Bibliography).

The medulla is much disorganized and shows cellular disintegration with scattered blood cells lying throughout its substance. Usually it is possible to detect in healthy glands the chrome-straining granules of the medullary cells. In the case of guinea-pigs fed on the scorbutic dietary these granules are few or altogether wanting.

I have been much impressed with the fact that the histo-pathological changes I have described were present in the adrenals of guinea-pigs, fed on the scorbutic dietary, which exhibited during life no clinical evidences of scurvy. Depression of adrenal function may, therefore, be regarded as a pre-scorbutic manifestation of a dietary deficient in accessory food factors of the 'C' class.

IV. SUMMARY

A scorbutic diet gives rise in guinea-pigs to:

(1) An increase in size and in weight of the adrenal glands;

(2) a marked diminution in the adrenaline content of these organs;

(3) haemorrhagic infiltration of the adrenal glands, usually circumscribed in extent and situated around the periphery of the adrenal cortex; and to

(4) degenerative changes in the cellular elements of the adrenal cortex and medulla.

V. CONCLUSIONS

(1) A scorbutic diet causes pronounced depreciation in functional capacity of the adrenal glands in guinea-pigs.

(2) The impairment of adrenal function occurs before clinical evidences of scurvy manifest themselves.

Histo-Pathology[1]

The present paper deals with the histo-pathological changes in the spleen, liver, pancreas, kidneys, pituitary body, and thyroids of pigeons fed exclusively on a diet of autoclaved milled rice. It is a continuation of a previous Report on the 'Pathogenesis of Deficiency Disease'[2], and is to be read in connection therewith. The histo-pathological changes in the intestines[3,4] and testicles,[2] of pigeons so fed have already been described.

I. THE SPLEEN

This organ is greatly atrophied. I am aware of no other morbid process in which such pronounced atrophy of the spleen occurs.

The histological changes consist in:

(1) Thickening of the capsule and contraction of the organ;

(2) atrophy of splenic pulp and partial disappearance of lymphoid cells;

(3) increased deposit of pigment; and,

(4) thickening of the walls of the arteries.

These make up a picture more remarkable than that presented by any other organ of the body, with the exception of the thymus, the testicles,[4] and the intestines.

In consequence of the atrophy of the splenic pulp and the reduction in numbers of the lymphoid elements of the organ, its fibrous trabeculae and arterial system stand out in sections with abnormal prominence. The capsule is much thickened and the organ contracted, both changes resembling closely those which occur in the testicles.[2]

The pigment in the atrophic spleen appears to be increased in amount. It seems probable that the increased blood destruction,[2] which occurs in consequence of the deficient diet, may to some extent be responsible for the increased deposit of pigment.

The lymphoid cells and the cells of the pulp are involved in a process of necrobiosis and absorption; they are greatly reduced in numbers. The nuclei lose their staining characters, a gradual karyolysis occurs and the cytoplasm ultimately disintegrates. In the more atrophic spleens, only traces of Malpighian corpuscles are to be found.

The vessels are involved in a process of proliferative arteritis, often

[1] Extract from number 71 in Bibliography.

[2] Number 67 in Bibliography.

[3] Number 74 in Bibliography.

[4] Number 69 in Bibliography.

leading to great thickening of their walls and to constriction of their lumen.

The thickening of the vessels suggests that the pathological changes may in some part be due to the prolonged action of toxic substances generated in the course of a highly abnormal metabolism.

II. THE LIVER[1]

This organ's loss of weight, is to a great extent masked by the congestion which usually accompanies it.

III. THE PANCREAS[1]

In contrast to the constant and fairly definite loss of weight, the histological changes in the pancreas are both inconstant and indefinite.

IV. THE KIDNEYS[1]

These organs lose little or no weight. Some degree of congestion is an almost constant feature. The cells may exhibit little or no change, or slight degrees of cloudy swelling may be present.

V. THE PITUITARY[1]

The glandular part of this organ tends to increase slightly in weight. Moderate congestion is the main histological change.

VI. THE THYROID[1]

The gland loses slightly in weight. Histological evidence of departure from normal is scanty.

VII. SUMMARY

In general, the histo-pathological changes found in uncomplicated cases in the various organs here dealt with are of two kinds: (1) necrobiosis, and (2) congestion. In some organs—the thymus, the spleen, and the testicles—the disappearance of tissue cells is the more prominent change. In others—the intestines, the liver, the pancreas, and the kidneys—congestion, with haemorrhagic infiltration, is often the more prominent feature, although there are exceptions to this generalization. In others again—the thyroids and the glandular part of the pituitary—both features may be present but usually in mild degree.

The haemorrhagic changes are the result in pigeons of passive congestion; the necrobiotic changes are in the main the result of malnutrition of the cells and more especially, I think, of nuclear starvation. Toxic irritation consequent, it may be presumed, on abnormal metabolic processes or on the action of ferments generated from necrobiotic cells may possibly contribute to them.

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[1] For further details see number 71 in Bibliography.

The extraordinary hypertrophy of the adrenal glands observed in pigeons fed exclusively on autoclaved rice will be considered separately.

VIII. CONCLUSIONS

(1) An exclusive diet of milled and autoclaved rice gives rise in pigeons to atrophic and congestive changes in the thymus, the spleen, the testicles, the intestines, the liver, the pancreas, the kidneys, the glandular part of the pituitary and the thyroid.

(2) These changes are most marked in the organs least essential to the life of the individual—the thymus, the testicles, and the spleen; in these atrophy is the predominant feature.

(3) The atrophic and congestive processes gravely affect the organs of digestion and assimilation and to a less extent the kidneys.

(4) The thyroid and the glandular part of the pituitary are less affected than are other organs of the body.

The Influence of a Scorbutic Diet on the Bladder[1]

The effects of a scorbutic diet on the bladder were studied in guinea-pigs. The animals, five in number, were fed on crushed oats and autoclaved milk. An equal number of controls were fed on crushed oats, autoclaved milk, and abundance of green vegetables.

A diet of crushed oats and autoclaved milk is deficient in accessory food factors of the 'C' class; it is probably also deficient in other substances essential for the maintenance of perfect health in guinea-pigs.

Those animals fed on the scorbutic diet died within periods varying from nineteen to twenty-nine days. Their average initial weight was 532 gm.; the average loss of weight amounted to 152 gm. One only developed clinical signs of scurvy; this animal had survived the deficient dietary for twenty-nine days. In two only were naked-eye evidences of a scorbutic state obvious at autopsy; one of these survived the deficient dietary for twenty-nine days, the other for twenty-five days. In all, haemorrhagic infiltration of the organs—the adrenals,[2] the kidneys, the liver, the intestines[3]—was present in greater or lesser degree on histological examination. The heart's blood of the guinea-pig which ex-

[1] Extract from number 72 in Bibliography.

[2] Number 70 in Bibliography.

[3] Number 69 in Bibliography.

hibited clinical evidences of scurvy yielded on culture at autopsy a coliform organism. The adrenaline content of the adrenal glands in this animal was excessively low.[1]

I. CLINICAL EVIDENCES OF DERANGEMENT OF THE BLADDER

Haematuria was observed in one animal only; in this the clinical evidences of experimental scurvy were well marked. In the four remaining animals haematuria was not observed. The urine was not examined microscopically; it seems probable, therefore, that a slight degree of haematuria may have occurred (*vide infra*) in one other case, although not detected clinically.

II. NAKED-EYE EVIDENCES OF DERANGEMENT OF THE BLADDER

At autopsy the bladder was empty and tightly contracted in all cases. In two cases it resembled an acorn set in a thick-lipped cup. This appearance was due to swelling of the tissues around the neck of the bladder.

Engorgement of the vessels with sub-peritoneal ecchymoses was a prominent feature in four cases. In some the congestion of the organ was more marked at its apex, in others at its base. On opening the bladder and examining the mucous surface with the hand lens, congestion of its mucous membrane, with patchy ecchymoses at various points, was present in greater or lesser degree in all cases. The congested and ecchymotic areas were of unequal distribution and of varying extent in different animals.

III. HISTOLOGICAL EVIDENCES OF DERANGEMENT OF THE BLADDER

The histological changes consisted in:

(1) Congestion of all coats, with haemorrhagic infiltration of the mucous membrane; and
(2) degenerative changes in the epithelium of the mucous membrane.

1. *Haemorrhagic Infiltration*

The vessels of the bladder walls were intensely engorged in four cases. Extravasation of blood corpuscles into the submucous and muscular coats and between the epithelial cells of the mucous membrane was an almost constant feature. This extravasation was of varying degrees of intensity in different animals and at different parts of the bladder wall; it was not present at every area of the mucous surface but was confined to certain points, the intervening areas showing little or none. In one animal haemorrhagic infiltration was found at only two points and was of lesser degree. In animals showing the lesser degrees of haemorrhagic infiltration, the infiltrating corpuscles either did not reach the marginal layer of epithelial cells, or having reached it were extruded into the lumen of the viscus in but small numbers. In the more pronounced degrees of haemorrhagic infiltration, blood corpuscles were extruded into the cavity of the bladder in larger numbers or in such quantity as to constitute actual haemorrhages. It will be noted that the haemorrhagic infiltration often caused the epithelial lining to bulge into the cavity of the bladder at the points where it occurred. The various stages in the haemorrhagic process are well shown in the photo-micrographs in the original paper.

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[1] Number 70 in Bibliography.

Congestion of the submucous and muscular coats was present in greater or lesser degree in all cases.

2. *Degenerative Changes in the Bladder Epithelium*

These consisted in:

(i) Swelling of the epithelial cells;
(ii) swelling of the nuclei of these cells and loss of their staining characters; and
(iii) desquamation of degenerated epithelial cells.

IV. COMMENTARY

Considered from the clinical point of view, these findings afford an explanation of the comparatively frequent occurrence of haematuria in human scurvy. They indicate that this symptom, which is usually a late manifestation of the scorbutic state in man, is the clinical evidence of an extreme degree of congestive and degenerative change in the mucous coat and epithelial lining of the bladder. They indicate also that congestive states of the bladder may occur in guinea-pigs, fed on a scorbutic diet, which exhibit no obvious clinical evidences of scurvy during life, and little or no naked-eye pathological evidences of this malady after death.

Congestion of the bladder without clinical evidence of haematuria may then be regarded as a pre-scorbutic process in guinea-pigs. This being so, a point of practical importance to the physician is to ascertain, by clinical and therapeutical observation, whether congestion of the bladder may not be so produced in man and if so whether certain abnormalities of micturition may not sometimes be evidences of a prescorbutic state in human beings, especially in children.

The Effects of Autoclaved Rice Dietaries on the Gastro-Intestinal Tract of Monkeys[1]

I. INTRODUCTION

The experiment with which the present paper deals had for its object the production of beri-beri in monkeys by means of dietaries of autoclaved rice.

For this purpose thirty-six young monkeys (*macacus sinicus*) were imported from Madras. The animals had recently been captured in the local jungles. With one exception, they were in perfect health. The exception occurred in the case of a monkey which died of general peritonitis one week after its arrival in Coonoor. Colonel Donovan, I.M.S., examined the peripheral blood in the majority of the animals; he found no blood parasites.

The monkeys were very wild and difficult to handle. After weighing, they were placed in separate cages and grouped as follows:

Group I. Control monkeys: twelve in number.
Group II. Monkeys fed exclusively on autoclaved rice: twelve in number.
Group III. Monkeys fed on autoclaved rice plus butter: eleven in number.

The diet of the control monkeys consisted at first of bananas, bread, milk and onions; monkey-nuts were subsequently added.

The milled rice, which formed the basal diet of Groups II and III, was picked by hand in order to remove as far as possible all grains having portions of adherent pericarp. It was then soaked for forty-eight hours in several changes of water. Finally, it was autoclaved at a temperature of 130° C. for one hour and a half.

The experiment commenced in the case of Groups I and II on 14th May 1919. The animals were fed at 10 a.m. and again at 5 p.m. They were watered one hour before meals. It was found that those in Group II could not eat more than 2 oz. of autoclaved rice at each meal. Four ounces of autoclaved rice *per diem* was, therefore, fixed as the ration for the animals in Groups II and III.

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[1] Extract from number 73 in Bibliography.

In the case of Group III, the experiment commenced on 2nd June 1919. Three pounds of autoclaved rice, prepared as above, were mixed by hand with 5½ oz. of fresh butter, giving a daily allowance of over 4 oz. of rice and ½ oz. of butter for each animal. The morning and evening feeds thus consisted of 2 oz. of autoclaved rice and ¼ oz. of fresh butter.

The average initial weight of the monkeys in Groups II and III was approximately 2 kg.; their daily allowance of rice (4 oz.) was, on this basis, much greater than that included in the rice ration of Indian jails.

In Group II, the exclusive diet of autoclaved rice was lacking in all classes of accessory food factors; it was also deficient in suitable proteins, in fats and salts, and was excessively rich in starch. In the case of Group III, accessory food factors of the 'B' and 'C' classes were wanting, while the diet was still ill-balanced with respect to proteins, carbohydrates and salts.

II. COURSE OF THE EXPERIMENT

For the first seven to ten days the animals in Groups II and III maintained good, or moderately good, appetites; during the first week they ate greedily, during the second they ate with less zest and began to leave much of their ration untouched. Later they exhibited a loathing for the food and either ate sparingly or refused to eat. They crumbled up the block of autoclaved rice, as if searching for more nutritious particles; finding none, they threw the mass from them. Finally, the animals retreated to the corner of their cages refusing to eat.

At this stage it was realized that the experiment must fail in its original object, viz. to produce beri-beri, and that the factor of inanition must play a leading part in the production of the resultant morbid changes. Nevertheless the trial was persisted in, in the case of fourteen animals, with the new object of observing the effects of malnutrition on animals closely allied to man. It is with these effects, in so far as they relate to the gastro-intestinal tract, that the present paper deals.

In the table (p. 157), the duration of the experiment, together with the initial and final weights of the animals, and the chief clinical manifestation of gastro-intestinal disorder exhibited by them, are shown.

III. CLINICAL EVIDENCES OF DISEASE

In addition to loss of body-weight, the main clinical evidences of disease exhibited by the animals in Groups II and III were:

(1) Progressive anaemia,

No. of Monkeys	*Sex*	*Original Weight (gm.)*	*Final Weight (gm.)*	*Loss of Weight (gm.)*	*Number of Days under Experiment*	*Diet*	*Clinical Evidences of Gastro-intestinal Disorder*
1	Male	2,000	1,500	500	19	Autoclaved rice	Diarrhoea becoming dysenteric
2	Female	1,350	950	400	26	,,	Diarrhoea becoming dysenteric (amoebic)
3	Male	1,470	1,040	430	22	,,	Diarrhoea
4	Female	1,570	1,170	400	22	,,	——
5	Male	1,900	1,400	500	24	,,	Diarrhoea becoming dysenteric (amoebic)
6	,,	1,380	980	400	19	,,	Ditto
7	Female	1,930	1,450	480	26	,,	Diarrhoea
8	,,	1,650	1,320	330	26	,,	Dysentery
11	Male	1,900	1,470	430	22	,,	——
12	,,	1,780	1,420	360	28	,,	Diarrhoea
27	,,	1,810	1,250	560	15	Autoclaved rice and butter	Ditto
29	Female	2,130	1,720	410	13	,,	Dysentery (amoebic)
30	,,	2 520	1,850	670	14	,,	Diarrhoea (sprue-like)
36	Male	2,410	1,800	610	18	,,	Ditto
13	Female	2,300	2,300	—	33	Normal food	Nil
20	Male	2,470	2,420	50	40	,,	Nil

NOTE. Although twelve control monkeys were kept under observation throughout the course of the experiment, two only were killed at its termination for purposes of comparison with those dying in consequence of the deficient diet. It was considered unnecessary to use more controls for this purpose.

(2) gastro-intestinal disorders, and
(3) progressive asthenia ending in death.

No clinical evidences of polyneuritis or of oedema were observed in any; in one case (No. 7), 1 c.c. of fluid was found in the pericardial sac at autopsy.

Gastro-intestinal disorder was evidenced by:

(i) Loss of appetite,
(ii) vomiting,
(iii) diarrhoea, and
(iv) dysentery.

(i) *The loss of appetite* was mainly due to loathing of the food. This loathing was accentuated by the gastro-intestinal derangements resulting from the deficient dietaries. The symptom is an important effect of vitaminic deficiency.

(ii) *Vomiting* was observed in four cases; it probably occurred oftener as the animals could not be kept under constant observation. The symptom did not persist for more than two days; the animals so affected refused all food and died rapidly.

(iii) *Diarrhoea* was the most constant symptom. It was present in ten out of fourteen animals. It made its appearance between the fourteenth and the twenty-fifth day of the experiment, and persisted either as a frank diarrhoea or merged into true dysentery. In six cases (see table, p. 157), the symptoms of diarrhoea persisted up to the time of death; in four they merged into those of true dysentery. The diarrhoeic motions were small, numerous and pale in colour, resembling pea-soup. Microscopical examination showed the stool to consist mainly of: (1) epithelial cells in various stages of disintegration, (2) enormous numbers of bacteria, and—in iodine-stained specimens—(3) a small amount of undigested starch. Amoebae, but without ingested red blood corpuscles, were present in one case. In animals (Group III) receiving butter in addition to the autoclaved rice, another feature was added to the microscopical characters of the stools: large amounts of fats and fatty acids were present. The stools in these cases were paler than usual, and in two instances distinctly frothy, resembling those of sprue.

(iv) *Dysentery*. Diarrhoea was preliminary to the onset of dysentery in four cases out of ten. After the lapse of a day or two, during which diarrhoeic stools were passed, the motions became mucoid and streaked with bright-red blood; later they consisted of pladgets of tough blood-stained mucus, sometimes intermingled with traces of pale yellow-white faecal matter but more often consisting solely of mucus mixed with blood. In two cases dysentery made its appearance without any preliminary diarrhoea. The familiar characters of dysenteric stools were obscured to some extent in these cases by the nature of the animal's food and by the small faecal output induced by the state of semi-starvation. Nevertheless, they were such as in the human subject would have suggested 'amoebic' dysentery to the mind.

Animals rarely survived the onset of dysentery for more than a few days. In two cases dysenteric stools were passed only for two days prior to the animal's death; in four others they survived the onset of dysenteric symptoms for four, five, six, and seven days respectively.

In the diagnosis of these cases I have had to limit myself to investigation of the microscopical characters of the stool. Bacteriological studies could not, unfortunately, be undertaken. I am, therefore, unaware of the extent to which bacilli may have been responsible for, or participated in, the production of the dysenteric symptoms. There were present in the stools enormous numbers of cellular elements of the most diverse form and size. These elements included, in addition to amoebae in some cases: (1) desquamated epithelial cells in various stages of disintegration, appearing singly or in connected groups of a dozen or more, (2) red blood corpuscles always in considerable numbers, (3) leucocytes and pus cells in large numbers, (4) single, double, and, more rarely, four-nucleated small round cells, and (5) large mononuclear cells ranging in size up to 25μ or even more. The majority of these cells showed degenerative changes.

In arriving at a diagnosis in any particular case I have followed the rule laid down by Wenyon and O'Connor[1] and called no case 'amoebic' unless I found 'at least some amoebae with included red blood corpuscles present, or definite *E. histolytica* cysts associated with the amoebae in the stool'. On this basis, four cases were classed as 'amoebic' dysentery. Amoeboid organisms of varying sizes up to 25μ were present in a fifth case, but as these did not contain ingested blood corpuscles, nor were associated with *E. histolytica* cysts, this case was not classed as 'amoebic'. In the sixth case no amoebae were found; the histological characters of the stool in this case were such as to render the diagnosis of bacillary dysentery legitimate on these characters alone.

In order to determine whether the monkeys had been amoebae carriers the faeces of eight healthy control animals were examined. One examination only was made. *E. tetragena* cysts were found after prolonged search in one case, blastocysts (considered by Flu[2] to be degenerative forms of *E. tetragena*) were found in moderate numbers in a second and in very large numbers in a third; *E. coli* were present in three others. No amoebae were found in the faeces of the two remaining control animals.

Throughout the greater part of the experiment twelve control monkeys remained free from gastro-intestinal disturbances of any kind. Towards its close, however, seven of them developed jaundice. A meagre diet of plantains and milk, to which was added a pinch of Epsom salts for a few days caused the jaundice to clear up. In no case did diarrhoea or dysentery occur.

It is possible that flies may have conveyed *E. tetragena* cysts or dysenteric bacilli from infected to non-infected animals in the same room. Since, however, the control monkeys did not suffer from dysentery—although equally exposed to any possible infection—it is

[1] Wenyon, C. M., and O'Connor, F. W., *J.R. Army med. Cps.*, 28, 1–34, 151–87, 346–70, 1917.

[2] Flu, P. C., *Meded. burgel. geneesk. Dienst. Ned.-Ind.*, 6, 113–16, 164, 1918.

obvious that the provision of a well-balanced dietary secured their immunity.

This observation indicates (1) that monkeys in the wild state in S. India may be carriers of *E. tetragena* (*histolytica*), and (2) that states of malnutrition favour the multiplication of pathogenic agents of dysentery present in the intestinal tract, whereas a satisfactory balanced dietary has the reverse effect.

Workers in the Tropics have long been familiar with the fact that cysts of *E. tetragena* (*histolytica*) may be present in the stools of perfectly healthy individuals, and absent from the stools in a proportion of cases possessing the clinical characters of the type of dysentery called 'amoebic' (Manson). I know of no work, however, designed to determine the percentage of *E. tetragena* carriers amongst natives of British India, although doubtless such exists; but recently Flu[1] has estimated that at least 10 per cent of natives of the Dutch Indies are *E. tetragena* carriers, and has concluded that this estimate is probably much too low. Wenyon and O'Connor[2] also have found 4·5 per cent of *E. histolytica* carriers amongst healthy British troops in Egypt who gave no history of dysentery. They found also that 13·5 per cent of healthy natives of Egypt were *E. histolytica* carriers. It appears, therefore, that *E. tetragena* (*histolytica*) may exist in the healthy intestine as a 'pathogenic saprophyte' without giving rise to dysentery until the conditions requisite for its growth upon and in the intestinal mucosa are provided by certain favouring circumstances. Amongst these circumstances, malnutrition—including deficiency of accessory food factors—is one. It appears probable also that bacillary dysentery is favoured in its origin by like circumstances.

These observations have a practical bearing in regard to the prevalence, prevention and cure of diarrhoea and dysentery. They provide an explanation of the occurrence of 'famine dysentery' so well recognized in India during times of food scarcity. The specific agents of dysentery, whether recently ingested or existing as 'pathogenic saprophytes', find in the malnourished state of the intestinal mucosa of famine-stricken individuals the conditions necessary for their unhampered growth. It is not necessary to assume a fresh amoebic infection in every case of amoebic dysentery, since the native of India, no less than *macacus sinicus*, may be considered to be often an amoeba carrier.

The frequent occurrence of dysentery amongst the starving inhabitants of certain occupied territories during the late war has probably a like explanation. No doubt both war and famine more often provide greater facilities for the entry of the specific micro-organisms of dysentery into the human intestine than do the more sanitary conditions of peace and plenty; but while recognizing this the present experiment brings into special prominence the importance of suitable dietaries in preventing the onset of this malady.

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[1] Flu, P. C., *Meded. burgel. geneesk. Dienst. Ned.-Ind.*, 6, 113–16, 164, 1918.

[2] Wenyon, C. M., and O'Conner, F. W., *J.R. Army med. Cps.*, 28, 1-34, 151–87, 346–70, 1917.

The demonstration of the influence of malnutrition in the causation of dysentery may have an important bearing on the prevalence of this malady in jails and asylums. The rice dietaries of Indian jails are, in those cases where I have ascertained their composition, often too close to the borderland of insufficiency with respect to their protein, fat and vitamine content. Thus in one jail in the Madras Presidency, the 'Rice Diet' consists of rice 20 oz., salt $\frac{3}{4}$ oz., tamarind $\frac{1}{2}$ oz., curry powder $\frac{1}{4}$ oz., oil (vegetable) $\frac{1}{2}$ oz., *dhal* 5 oz., vegetables 6 oz. The rice is polished and lacks an adequate supply of accessory food factors of the 'B' class. This deficiency may, to some extent, be compensated for by the 5 oz. of *dhal*, provided that the *dhal* is not deprived of its germ and pericarp. But, in southern India, so far as I can ascertain, *dhal* (*arhar*) without its pericarp is chiefly eaten. In northern India '*Dhal Urd*' (Bengal gram) and '*Mung dal*' are used—in these the pericarp is retained. Half an ounce of vegetable oil does not provide a sufficiency of fats or of accessory food factors of the 'A' class, while accessory factors of the 'C' class, contained in the vegetable components of this dietary, are probably largely destroyed in the process of cooking. Such a ration is, therefore, too rich in carbohydrates and too poor in animal fats and proteins, while there is too small a margin of safety with respect to its 'vitaminic' content. It seems probable that 'jail dysentery' may to a great extent be capable of prevention by the more generous and judicious use of appropriate articles of food.

The cessation of this experiment afforded me an opportunity to observe, on the substitution of an adequate dietary, the rapid disappearance of diarrhoea (and of dysentery in one case) in monkeys reduced to a grave state of asthenia by the deficient dietary. In the treatment of dysentery it is necessary to take care that the milk-and-rice-water dietaries so commonly employed are not lacking in vitamines. If they are, not only will recovery from the dysenteric process be greatly impeded but symptoms of beri-beri will be prone to manifest themselves. The literature contains many examples of the association of dysentery with beri-beri due largely to these causes.

IV. PATHOLOGICAL EVIDENCES OF GASTRO-INTESTINAL DISEASE

The animals were, for the most part, autopsied immediately after death. Where this could not be done the bodies were placed in cold storage and a post-mortem carried out twelve to eighteen hours later. In thirteen cases, the heart's blood was cultured by aerobic methods at autopsy. Growths were obtained in five cases; with one exception autopsy was performed in these cases immediately after death. The organisms recovered from the blood—usually coliform organisms and small cocci—no doubt indicated the presence of so-called 'terminal' infections. It was noted, however, that the adrenaline content of the adrenal glands was considerably lower in septicaemic cases than in the majority of animals from whose heart's blood no organism was grown. In the former the average adrenaline content was 0·00026 gm., in the latter 0·00039 gm. This circumstance suggests that haemic infections existed in the former cases some considerable time prior to death and probably hastened it. As will be seen, the diseased state of the gastro-intestinal tube is such as to render haemic infections extremely likely to occur.

1. *External Appearances of the Gastro-Intestinal Tract*

On opening the abdomen it was observed that the abdominal wall was greatly thinned and completely devoid of fat. The glands of the groin were often enlarged. The omentum existed as a thin, transparent membrane from which all traces of fat had disappeared. In healthy monkeys it was found to weigh from 50 to 56 gm., while in monkeys dying in consequence of the deficient food it weighed but 3 to 4 gm.; the loss of weight was due mainly to loss of omental fat. Its vessels were rarely engorged. It closely enveloped the whole mass of intestines being snugly tucked underneath their lower border at the level of the pelvis.

The mesentery also was excessively thinned, but its vessels were rarely engorged. The mesenteric glands, especially those of the colonic mesentery, were invariably much enlarged. In healthy monkeys these structures can just be distinguished by the naked eye as small, oval, pink bodies lying at the attachment of the mesentery with the bowel; their size in health did not appear to exceed that of a canary seed, except internal and posterior to the caecum where they were sometimes as large as a hemp seed or even of a small pea. In monkeys dying in consequence of the deficient dietary the mesenteric glands ranged in size from that of a hemp seed to that of a haricot bean. Especially in the vicinity of the caecum they were found to be very prominent. Posterior and internal to this part of the viscus a large mass of greatly enlarged and often discoloured glands was invariably found. In colour they varied from a pale pink to a dull grey or a dark slate-grey colour; in some cases they were of a grey-black tinge. There is no more prominent morbid anatomical feature in these cases than the great enlargement, and the frequent discolouration, of the colonic mesenteric glands; it is an indication of the intense degree of toxic absorption (with which may be included bacterial migration) which takes place from the diseased bowel in these cases. In only one case were the enlarged mesenteric glands examined by cultural methods: a coliform organism, in association with a small coccus, was obtained in this case by aerobic methods of culture.

The stomach was invariably greatly dilated and its walls much thinned. It but rarely showed external evidences of congestion.

The small intestine was always greatly thinned, either throughout its whole extent or more particularly at certain areas. Ballooning of the small bowel was present in eight cases out of fourteen. The ballooning occurred usually in the ileum. The ballooned areas were as a rule multiple and of varying extent; in some cases they were confined to an inch or two of the bowel, in others much larger areas were involved. In one case (butter-fed), the whole gastro-intestinal tract from the stomach to the rectum was greatly ballooned. The ballooning was not due to the accumulation of intestinal contents at these areas but to excessive thinning of the bowel walls.

Intussusception was present in ten cases out of fourteen. The invaginations were usually multiple, invariably descending—the upper portion of the bowel being invaginated into the lower—often of small size, and never showing evidences of inflammation. They were found at all parts of the small intestine from the jejunum downwards; in one case only was the intussusception ileo-caecal. The majority of these intussusceptions were no doubt manifestations of the death agony. In some, however, although no inflammatory changes had occurred, considerable constriction was present; the invaginated bowel being then much engorged and sometimes of a reddish-brown hue. It is concluded that such invaginations occurred at least several hours prior to death. I am disinclined to regard them as wholly agonal in origin; agonal intussusceptions are said to be usually ascending, those in the present experiment were invariably descending. It appears probable that the changes in the neuro-muscular mechanism of the bowel, presently to be described, are concerned in their origin.

Congestion of the small intestine was usually a prominent feature;

small ecchymoses were frequently found widely distributed under the serous coat. Sometimes these ecchymoses involved the small bowel in its entire length; sometimes they were limited to the duodenum or to the lower end of the ileum or both. As a rule, the congestive process was more marked in the duodenum than in other parts of the small intestine. A notable feature in monkeys fed on autoclaved rice plus butter was the pale yellow-white colour of the entire gastro-intestinal tube.

On opening the abdomen, the external evidences of disease presented by the large intestine were the following: (1) congestion and subperitoneal ecchymoses, (2) ballooning, (3) thinning and partial disappearance in places of the longitudinal bands of muscle.

The congestive process affected the great bowel in the same manner as the small. Sometimes subserous ecchymoses occurred throughout its entire length from the tip of the caecum to the lower end of the rectum. More usually the ecchymoses were limited to certain areas, frequently to its last four to six inches. Occasionally grey-black lymphoid nodules of the size of a small pea projected into the serous coat. The colons of butter-fed monkeys were usually of a pale yellow-white tint in marked contrast to the pink tinge of health.

The ballooning of the colon affected in rare cases the whole organ from the caecum downwards. As a rule, however, it was limited to certain areas. At these areas the characteristic puckerings of the great bowel, produced by the three longitudinal bands of muscular fibres, were wanting or much less prominent than in health. The bowel walls were greatly thinned, the longitudinal bands of muscle being less evident than in health: sometimes the naked eye could only detect with difficulty the longitudinal bands at these areas; then they seemed to terminate abruptly at the upper extremity of the ballooned area and to commence again at its lower. When placed in formalin, however, the thinned bands could be clearly seen. As a rule, the ballooned areas involved the whole circumference of the bowel, but occasionally they were limited to one side of the bowel resembling, then, a weak spot in an inflated inner cycle tube. They were not due to faecal accumulations. Between these ballooned areas the colon often presented a comparatively normal appearance with respect to its longitudinal bands and puckerings.

The external appearances of the gastro-intestinal tract thus presented evidences of grave derangement of bowel function.

2. *Internal Appearances of the Gastro-Intestinal Tract*

The stomach was always greatly distended and quite empty. The hand lens showed its mucous membrane to be abnormally soft and necrotic. Ecchymoses were frequently present; usually at the pyloric end of the viscus. They varied in extent and in degree; in one case the whole mucous membrane of the stomach, with the exception of a small portion of the fundus, was covered with minute ecchymoses. In thirteen cases no ulcers were present; in the fourteenth an ulcer of the size of a threepenny bit was present at the pyloric area.

(i) THE DUODENUM

Congestive and necrotic changes in the mucous membrane were the chief features observed in this part of the bowel; these changes were often very marked. No ulcers were met with. As a rule, the ecchymoses of the mucous membrane were much more pronounced in the duodenum than in the stomach and were sometimes seen to commence sharply, or more properly to be sharply accentuated, at the distal side of the pylorus. The whole surface of the duodenum was often studded with small pin-point haemorrhages, the mucous membrane appearing as if it had been dusted with pepper. The upper part of the duodenum was, as a rule, more severely affected than the lower.

The congestion and ecchymoses frequently extended to the jejunum and ileum, and in exceptional cases this 'peppered' appearance of the bowel was continued to the ileo-caecal junction. More usually, however, the congestion and ecchymoses were confined to the upper part of the small intestine or to the lower ileum, the intervening areas being comparatively free except where intussusceptions had occurred. In general, the invaginated portions of the bowel were more congested than other parts of the small intestine—the duodenum excepted—the congestion in some intussusceptions being pronounced. Above areas where the more extensive invagination of the bowel had occurred its lumen was often filled with a mucoid material resembling in appearance thin glue; this material was only present above the larger, and apparently older, intussusceptions where it was sometimes blood-stained. Where ballooning had occurred, the walls of the bowel were often so thin as to be transparent, and here also a thin glue-like mucoid material was sometimes present in the bowel lumen. Often, however, these areas were empty of all contents except gas.

As a rule, the naked-eye changes were more pronounced in the large intestine than at any other part of the gastro-intestinal tract—the duodenum excepted. The changes were those of an intense colitis but without ulceration. Although amoebic dysentery was present in a number of cases dying in consequence of the deficient dietary, no localized ulceration had occurred in any of them. The colitis sometimes involved the whole extent of the colon, but more usually it was confined to the last six inches of the great bowel; it usually corresponded in distribution to that of the subserous ecchymoses. In one case it assumed its maximum proportion at an isolated area of the mid-colon. The mucous membrane of the caecum was usually moderately congested and ecchymotic and often of a dark slate-grey colour. The lymphoid nodules of the colon were sometimes very prominent; in two cases they formed dark masses, the size of a small pea, which projected into the lumen of the bowel and into its serous coat; one of these nodules showed on section numerous collections of small cocci. At areas where ballooning had occurred the walls of the colon were excessively thin, often almost transparent. On opening the bowel at these points the walls collapsed like a burst balloon.

It is of interest to record the fact that amongst sixteen wild monkeys in which the gastro-intestinal tract was minutely studied at autopsy neither nematodes nor other intestinal parasites were found.

In connection with the pathological processes initiated in the gastro-intestinal tract of monkeys by an autoclaved rice dietary, the post-mortem appearances found in two cases of beri-beri by Willcox[1] during the Dardanelles campaign may be quoted: 'The stomach showed marked redness of the mucous membrane, which was most marked in the pyloric half where the colour was deep crimson. The duodenum showed intense crimson congestion of the mucosa, most marked in the upper part. The jejunum and ileum showed marked congestion, some petechiae being present in the ileum. The large intestine showed congestion. Numerous small haemorrhagic patches about half an inch in diameter were present in the wall of the ascending colon. The mesenteric glands showed slight enlargement.' The similarity of these changes to those found in monkeys fed on autoclaved rice is very noteworthy.

3. *Histo-Pathology*

The histo-pathological changes were studied in all fourteen cases and were contrasted with the normal appearances in healthy monkeys.

In order to avoid post-mortem changes in the tissues, portions of the cardiac and pyloric ends of the stomach, of the duodenum, of the jejunum, of the lower ileum, of the ballooned areas of the small intes-

[1] Willcox, H. W., *Lancet*, i, 553–7, 1916.

tine, of the colon and of the ballooned areas of colon were taken for histological study in each case as soon after death as possible. The tissues were fixed in Zenker's fluid and stained by Mann's stain, Unna's methylene blue and eosin, and Heidenhain's iron-haematoxylin.

The histo-pathological changes comprised:

(i) congestion and haemorrhage,
(ii) atrophy of the myenteron,
(iii) degenerative changes in the myenteric plexus of Auerbach,
(iv) atrophic, necrotic and inflammatory changes in the mucous membrane,
(v) bacterial invasion of the bowel walls, and
(vi) partial disappearance of lymphoid elements of the mucous membrane.

(i) CONGESTION AND HAEMORRHAGE

Where congestion occurred it was confined to the mucous, submucous and serous coats of the stomach and bowel. The myenteron was not involved or but slightly. In this respect the appearances presented by sections were in marked contrast to those previously described in the case of pigeons and guinea-pigs.[1] Small collections of effused blood corpuscles were frequently encountered under the serous covering of the bowel—usually in sections from the duodenum and colon. It is to be noted that congestion did not occur uniformly throughout the entire digestive tube; it was less marked in the mid-portion of the small intestine. The vessels of the duodenal and colonic submucosa were engorged and actual haemorrhages around the bases of the glands of Lieberkühn were not uncommon. Free blood corpuscles were often met with lying amongst the necrotic cells of the mucous membrane in sections from the stomach, duodenum and colon. The photo-micrographs illustrating the appearances seen in the diseased mucous membrane of the stomach sufficiently exemplifies this point.

(ii) ATROPHY OF THE MYENTERON

This atrophy varied in degree at different parts of the bowel. It was extreme in areas where ballooning had occurred. The dilatation of the stomach was probably less a matter of atrophy of its muscular coats than of their inability to contract. Apart from the ballooned areas of the bowel, where the myenteron presented extreme degrees of tenuity, the most remarkable changes were found in the longitudinal bands of the colon. The degree of thinning of these bands was shown in striking contrast by sections taken from approximately the same part of the colon in the healthy as in the diseased state.

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[1] Number 69 in Bibliography.

(iii) DEGENERATIVE CHANGES IN THE MYENTERIC PLEXUS OF AUERBACH

In all parts of the gastro-intestinal tract the ganglia of the myenteric plexus often presented appearances in marked contrast to those of health. Although the stains employed were not such as to bring out in minute detail the degenerative changes in individual cells, nevertheless they were sufficient to indicate the existence of such changes. The ganglia were much more prominent in the diseased bowel. In sections of the healthy intestine, examined under the microscope, the chain of ganglia lying between the longitudinal band and the circular layer of muscle could be seen with difficulty, whereas in the diseased bowel it was a prominent feature. The ganglionic cells were swollen, the cell membrane indistinct, frayed or wanting. The nuclei had often disappeared or existed only as fragments of chromatin; where complete nuclei were found they were often swollen. The nucleolus was frequently fragmented. Occasionally lacunae empty of cells were found in the degenerating ganglia. Ganglia were sometimes encountered in which no cell contained a normal nucleus; others in which a few cells appeared relatively normal, and other in which degenerative changes were slight or absent. There can be no doubt that such changes would impair the neuromuscular control of the bowel.

(iv) NECROTIC AND INFLAMMATORY CHANGES IN THE MUCOUS MEMBRANE

These consisted in necrosis of all cellular elements of the mucous membrane. The necrosing cells were often surrounded by inflammatory cells and effused blood corpuscles. The duodenum and colon were in general most severely affected in this regard; some degree of colitis was present in the great majority of cases. The mucous membrane of the stomach often exhibited necrotic and congestive changes. In ballooned areas of both small and large bowel, only remnants of mucous membrane were met with. All glandular elements of the gastro-intestinal tract were affected in greater or lesser degree—the gastric and pyloric glands, the glands of Brunner in the duodenum, the mucous glands of the colon and the glands of Lieberkühn. Throughout the entire intestinal tract the muscularis mucosae was greatly thinned, the atrophy in places constituting actual breaches in its continuity. The photomicrographs illustrate the appearances seen so clearly that no further description of them is called for.

Considerable variation in the severity of the lesions in different animals and in different parts of the same gastro-intestinal tract was noted.

(v) BACTERIAL INVASION OF THE BOWEL WALLS

This was encountered in a number of suitably stained specimens, especially from the colon. Bacteria in large numbers were often seen deep in the mucous membrane; sometimes they formed a bacterial capsule around the desquamated cells of the glands, as, for example, around those of the mucous glands of the colon. Frequently they were seen scattered throughout the submucosa, and mycelium-like organisms were, in several specimens, found lying in small cavities in this coat of the bowel. In some sections from the colon the bacterial invasion was seen to extend to the muscular layers, and bacteria in considerable numbers were found lying in and between the layers of the myenteron. More rarely, organisms were found in the serous coat or in blood-vessels. Large collections of cocci were found in an enlarged lymphatic nodule taken from the colon. The organisms, as seen in sections of the colon, were of four varieties: (1) cocci, (2) short rods, resembling *B. coli*, (3) longer rods, usually found in and between the muscular coats, and (4) mycelium-like organisms and their spores, usually found in small cavities in the submucosa.

(vi) ATROPHY OF LYMPHOID ELEMENTS

Although in the colon the lymphoid nodules were frequently swollen, in general the lymphoid elements of the intestinal mucous membrane were greatly reduced in numbers. In health the lymphoid cells are very abundant, whether collected into nodules or filling in the spaces between the glands of Lieberkühn. The thinning of the protective layer of lymphocytes no doubt facilitated the development of infective processes in the mucous membrane.

Clearly all these changes are such as would favour greatly haemic infection from the diseased bowel.

V. SUMMARY OF RESULTS

The effects of autoclaved rice dietaries on the gastro-intestinal tract of monkeys may be summarized as follows:

(1) Congestive, necrotic and inflammatory changes in the mucous membrane of the entire tract.

(2) Degenerative changes in the neuro-muscular mechanism of the

entire tract, leading to dilatation of the stomach, ballooning of areas of the small and large bowel, and probably also to the intussusceptions which so frequently occur.

(3) Pronounced necrotic changes in the secretory elements of the entire gastro-intestinal tract—of the gastric glands, the pyloric glands, the glands of Brunner, the glands of Lieberkühn, and of the mucous glands of the colon. These changes are such as must cause grave derangement of the digestive and assimilative processes.

(4) Intense toxic absorption from the diseased bowel as evidenced by the changes in the colonic mesenteric glands.

(5) Impairment of the protective resources of the entire gastro-intestinal mucosa against infecting agents, leading to infection of the mucous membrane by 'pathogenic saprophytes' and by ingested pathogenic organisms. These infections give rise to gastritis, enteritis, and to colitis, and frequently to haemic infections. The occurrence of dysentery in these circumstances is a most significant finding.

These results are very similar to those I have described in pigeons and guinea-pigs fed on ill-balanced dietaries deficient in accessory food factors.[1]

VI. COMMENTARY

Such degrees of malnutrition as those brought about under the conditions of the present experiment are rarely encountered during peaceful phases of our civilization. But the late war afforded many examples of gastro-intestinal disorder (amongst refugees, prisoners of war in Germany and Turkey, and the starved inhabitants of certain occupied countries) which find their pathological explanation in the facts here recorded. These facts represent an extreme picture: the end results of malnutrition. But between this extreme on the one hand and perfect nutrition on the other, there are intervening degrees of malnutrition which must determine the departure from health of the gastro-intestinal tract. It is with the 'mean' rather than with the 'extreme' that the physician is mainly concerned; with the long-continued use of imperfectly balanced and deficient food rather than with the lack of victuals; with the beginnings of disease rather than with its end results.

In the present experiment the gastro-intestinal lesions I have described were initiated by dietaries too rich in carbohydrates and too poor in other essential attributes of a perfectly balanced ration. With this combination the physician is familiar in the dietaries of human beings. It may be expected, then, that gastro-intestinal lesions of like kind, if not of like degree, will result in man from the continued use of such dietaries.

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[1] Number 69 in Bibliography.

To maintain the gastro-intestinal tract in health, and to enable it to protect itself and the body generally against invasion by ingested pathogenic organisms, it is necessary to provide from birth onwards a satisfactorily balanced dietary containing a sufficiency not only of proteins, calories and salts but also of accessory food factors of all three classes.

The General Effects of Deficient Dietaries on Monkeys[1]

I. INTRODUCTION

In another place I have recorded the effects of certain deficient and ill-balanced dietaries on the gastro-intestinal tract of monkeys.[2] It is the purpose of the present paper to summarize their general effects, reserving for a future report an account of the histo-pathological changes in the internal organs.

The dietaries employed were the following:

(1) A control diet consisting of wheaten bread, plantains, milk, fresh onions, and ground-nuts. Nine monkeys were fed throughout the course of the experiment on this dietary.

(2) An exclusive diet of autoclaved rice: that is to say, one deficient in suitable protein, in fat, in accessory food factors of all three classes and excessively rich in starch. Ten monkeys were fed to the point of death on this diet.[2]

(3) A diet of autoclaved rice and butter: that is to say, one deficient in suitable protein, in accessory food factors of the 'B' and 'C' classes and excessively rich in starch as well as in fat. Four monkeys were fed to the point of death on this diet.[2]

(4) A diet of autoclaved food (rice, wheaten bread, milk, and ground-nuts) to which a small ration of fresh onion was added: that is to say, a diet deficient in accessory food factors of the 'A' and 'B' classes. Six monkeys are included in this category.

(5) A diet of autoclaved food (rice, wheaten bread, milk, and ground-nuts) to which fresh onion and fresh butter were added: that is to say, a diet deficient only in accessory food factors of the 'B' class and excessively rich in fats. Five monkeys are included in this category.

Attention is directed to the composition of these dietaries. Their balance, or lack of balance, with respect to proteins, carbohydrates, and fats requires consideration as much as does their deficiency in vitamines. We shall see from the results of the experiments that they emphasize the importance of studying the 'dietetic history' in every case of gastro-intestinal disorder or of vague ill health in the human subject. And in so doing it would seem to be essential not to dissociate any existing deficiency of vitamines from other obvious defects, such as an insufficient supply of proteins or an excess of starch or of fats. For, it is to be remembered that deficiency of vitamines of the 'B' class often runs parallel with the excessive richness of starch in a diet, especially so when the source of the starch is polished rice, white flour, white bread, sago, tapioca and many proprietary foods. A dietary excessively rich in starch thus often connotes a deficiency of 'B-vitamine'. Now we shall see from the findings presently to be recorded what the effects of deficiency of this vitamine are in monkeys, and from these we are justified in assuming in similar circumstances like results in man. In man, however, it is not with complete vitaminic deficiency that we have most often to deal in practice, but with incomplete vitaminic deficiency. For the former causes rapid dissolution and death, the latter protracted disssolution and disease. It will be noted, moreover, that 'neuritic' lesions are by no means the most important of the effects of deficiency of 'B-vitamine'. Unfortunately, the adjective 'anti-neuritic' has been attached to accessory food factors of the 'B' class, so that a deficiency of this factor suggests the onset of 'polyneuritis' or of 'beri-beri' as its sole results. These, however, are but the grosser and later manifestations of such deficiency. The changes in the nervous system to which want of this vitamine gives rise are not its most important effects with respect to time of onset, to frequency of occurrence, and to need for recognition. It is true that lack of 'B-vitamine', associated as it usually is with an insufficient supply of protein and an excess of starch, may ultimately lead to degenerative changes in nerve cells, but of greater practical importance is it to recognize that this combination of defects in human dietaries may be expected to lead more early and more often to degenerative changes in, and to depression and failure of function of, those cells upon which the processes of digestion and assimilation are dependent. It is possible that the depression of function so induced may be accountable for a number of the commoner gastro-intestinal disorders, to which no bacterial or parasitic label has so far been attached. However this may be, the present records are offered as a contribution to their study. It will surprise those who investigate the 'dietetic history' of cases of chronic gastro-intestinal disorder to find how many persons habitually subsist on 'bread and butter' and 'milk puddings'. Such a dietary is poor in 'B-vitamine' and in protein, as well as excessively rich in starch and fats. It is my own experience in India that the 'dietetic history' of European sufferers from chronic colitis, and of those suffering from chronic gastro-intestinal disorders, commonly reveals the fact that their food does not contain the requisite proteins or the due proportion of starch, fats, salts, water and vitamines necessary for the maintenance of health. This one cannot 'digest' vegetables, fruit or meat or 'never touches them in India', that one can 'carry on only on farinaceous food'. So it is that the form of diet which they commonly adopt is that often most calculated to promote the very disorder from which they seek relief. As we shall see from a perusal of these records, the cardinal effects of deficient and ill-balanced dietaries in monkeys are gastro-intestinal disorder, dilatation of the stomach, gastritis, and colitis. They are likely to be the same in man. It did not surprise me, therefore, to find that a patient, who consulted me recently, and who for ten years has subsisted mainly on milk puddings, had a dilated stomach, air-locks in the small bowel which caused her great discomfort, delay in the passage of the intestinal contents, colitis, a tender caecal region, and an inefficient pancreas with glycosuria. The results of these experiments have helped me to visualize the changes which are likely to be occurring in the gastro-intestinal tract in such a chronic invalid. I desire, therefore, at the very outset of this report to emphasize the importance in practice of a study of the dietetic history in such cases believing, as I now do, that bacterial agencies are often but weeds which flourish in soils made ready for them by dietetic defects, and believing also that in the fuller comprehension of the science of dietetics we shall understand more perfectly the beginnings of disease and more fully its therapy.

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[1] Extract from number 74 in Bibliography.

[2] Numbers 73 and 74 in Bibliography.

II. DETAILS OF THE EXPERIMENTS

(1) The rice employed in these experiments was Bellary milled rice. It was picked by hand to remove all grains having portions of adherent pericarp. It was then soaked in several changes of cold water for forty-eight hours, with the object of extracting a proportion of water-soluble accessory food factors. Finally, it was drained and autoclaved at a temperature of 130° C. for one hour and a half. It has been found that prolonged autoclaving at a temperature of 130° C. is necessary in order to destroy effectually accessory food factors present in milled rice. The autoclaving of rice in bulk at a temperature of 130° C. for three-quarters of an hour does not appear to be sufficient to destroy all the 'B-vitamine' which it may contain. Pigeons fed on rice so autoclaved survive longer than do those fed on rice autoclaved at the same temperature for double the length of time.

(2) The autoclaved food employed in the experiments consisted of bread (*chapatties*) made from wholewheat flour, milk, ground-nuts, and Bellary rice. These articles were subjected in the autoclave to a temperature of 130° C. for one and a half hours—a treatment which, it may be presumed, completely destroyed their 'vitaminic' ingredients. Fresh butter and fresh onions, when added to food so autoclaved, provided accessory food factors of the 'A' and 'C' classes and other substances of nutritive value. The added butter, however, rendered the dietary, for wild monkeys, disproportionately rich in fats—a circumstance which was not without influence on the animals so fed.

(3) The scale of rations provided for the monkeys in the five categories was as follows:

(i) (Controls) bread 120 gm., milk 120 c.c., ground-nuts 10 gm., fresh onion 5 gm., fresh butter 2 gm., plantains 2, water.
(ii) Autoclaved rice 120 gm., water.
(iii) Autoclaved rice 120 gm., fresh butter 15 gm., water.
(iv) Autoclaved bread 60 gm., autoclaved rice 60 gm., autoclaved milk 120 c.c., autoclaved ground-nuts 10 gm., fresh onion 5 gm., water.
(v) Autoclaved bread 60 gm., autoclaved rice 60 gm., autoclaved milk 120 c.c., autoclaved ground-nuts 10 gm., fresh onion 5 gm., fresh-butter 15 gm., water.

The ration supplied to the animals in categories (ii), (iii), (iv), and (v), was the maximum amount a healthy monkey would eat. It was found that a monkey in vigorous health could not consume more than 120 gm. of autoclaved rice daily. This amount was therefore fixed as the ration for animals in categories (ii) and (iii). When their appetites began to fail they consumed only a portion of it.

(4) The monkeys (*macacus sinicus*) were captured in the jungles of Madras. The experiments were commenced within a fortnight of their capture. Those fed exclusively on autoclaved rice were mostly adolescent animals. Those fed on autoclaved rice and butter were adults, as were the controls and also those fed on autoclaved food, butter, and onion. Of those fed on autoclaved food and onion three were adults, while three were young, two of the latter still being with their mothers, although well beyond the stage of suckling. In both instances the mother and her young were confined in the same cage and received the same food.

(5) The dimensions of the cages used were 24″×15″×14″. Very little movement was, therefore, possible. Minute attention was paid to the general hygienic conditions under which the animals lived. When necessary the animal room was heated to an appropriate temperature by night, and the animals were protected from cold and draughts by thick

curtains drawn at night around the shelves on which their cages were placed. These precautions were necessary since the monkeys, whose natural habitat was the warm, moist climate of the east coast of India, were extremely susceptible to cold at an altitude of 6,000 feet above sea-level. The precautions were successful in preventing the death of any animals from causes attributable to climatic conditions. Two only were excluded for causes other than those directly attributable to the deficient dietaries. In one case an animal died on the seventh day of feeding on autoclaved rice; the cause of death was peritonitis. It is possible that it was injured during capture. A second animal amongst the controls was found at autopsy to have cystic disease of the kidneys and extensive consolidation of the lungs. Neither animal is shown in the table (p. 176).

(6) Three cases (monkeys Nos. 9, 25, and 26) included in the autoclaved food and onion category, require special mention. Monkey No. 9 was fed for twenty-eight days exclusively on autoclaved rice. Towards the end of this period it suffered from loss of appetite, vomiting, and diarrhoea. It exhibited also marked 'weakness' of the right leg. It was decided to attempt to prolong its life; its dietary was consequently enriched with whole-wheat-flour bread. This it seized upon greedily, refusing to eat the autoclaved rice. Its health improved markedly, it looked much better and the diarrhoea ceased. At the end of one week, during which it had received wheaten-flour bread, it was placed on dietary (iv), i.e. on autoclaved wheaten bread, rice, milk, and ground-nuts, with a small ration of fresh onion. It survived this dietary for a further period of fifty-two days, when it died. The right leg became more obviously affected as the experiment progressed, so that the animal kept it constantly flexed and refrained from placing it on the floor of its cage. Towards the end of the experiment it became excessively anaemic, losing its appetite a week to ten days before death, and finally died of asthenia. Marked degeneration of peripheral nerve fibres was found on microscopical examination. Monkeys Nos. 25 and 26, mother and young, were fed for sixteen days exclusively on autoclaved rice, and subsequently to the end of the experiment on autoclaved food and onion.

(7) Monkeys Nos. 28, 31, 32, 33 and 34 were fed for the first ten days on autoclaved rice and butter, and subsequently on autoclaved food with butter and onion.

III. DURATION OF THE EXPERIMENTS

In the following table the duration of the experiments, the dietary employed in each case, the sex of the animals, and their initial and final body-weights are shown:

	No. of Monkeys	*Sex*	*Original Body-weight (gm.)*	*Final Body-weight (gm.)*	*Percentage Gain or Loss in Weight*	*Days under Experiment*	*Dietary Employed*
Controls	13	Female	2,300	2,300	±0	33	Fresh bread, milk, onion, plantains, ground-nuts, water.
	15	,,	2,680	3,050	+13	92	
	16	,,	2,740	2,300	−17	106	
	17	Male	1,780	1,900	+6	106	
	18	,,	2,320	2,170	−7	104	
	19	Female	2,420	2,200	−10	104	
	20	Male	2,470	2,420	−2	101	
	24	,,	2,170	2,120	−3	101	
Experi-mental Animals	1	Male	2,000	1,500	−25	19	Auto-claved rice, water.
	2	Female	1,350	950	−30	26	
	3	Male	1,470	1,040	−30	22	
	4	Female	1,570	1,170	−26	22	
	5	Male	1,900	1,400	−27	24	
	6	,,	1,380	980	−29	19	
	7	Female	1,930	1,450	−25	26	
	8	,,	1,650	1,320	−20	26	
	11	Male	1,900	1,470	−23	22	
	12	,,	1,780	1,420	−21	28	
	27	Male	1,810	1,250	−31	15	Auto-claved rice and fresh but-ter, water.
	29	Female	2,130	1,720	−20	13	
	30	,,	2,520	1,850	−27	14	
	36	Male	2,410	1,800	−26	18	
	9	Male	2,090	1,320	−37	82	Auto-claved[1] food and fresh onion, water.
	21	,,	1,280	900	−30	67	
	22	Female	1,850	1,200	−36	67	
	25	,,	1,190	850	−29	62	
	26	,,	2,760	1,820	−35	51	
	35	Male	1,320	1,050	−21	98	
	28	Male	2,720	1,700	−38	100	Auto-claved[1] food, fresh butter and onion, water.
	31	,,	2,250	1,410	−38	71	
	32	Female	2,400	1,950	−19	51	
	33	Male	2,030	1,590	−22	43	
	34	Female	2,710	1,900	−30	80	

It is seen from this table: (a) that monkeys fed exclusively on autoclaved rice died, or reached the point of death, in periods ranging from 19 to 28 days, or in an average period of 23·4 days; (b) that monkeys fed on autoclaved rice plus butter died, or reached the point of death, in periods ranging from 13 to 18 days, or in an average period of 15 days; (c) that monkeys (Nos. 21, 22, 25) fed on autoclaved food plus a small ration of fresh onion died, or reached the point of death, in periods ranging from 67 to 98 days, or in an average period of 77·3 days; (d) that monkeys fed on autoclaved food plus fresh butter and onion died, or reached the point of death, in periods ranging from 43 to 100 days, or in an average period of 65 days; (e) that control monkeys fed on a well-balanced dietary suffered, as a rule, no ill effects other than those contingent on confinement in small cages. It appears, therefore: (1) that monkeys (*macacus sinicus*) cannot sustain life for much longer than 30 days on an exclusive diet of rice which has been autoclaved at a temperature of 130° C. for one and a half hours; (2) that the addition of fresh butter to the dietary of rice so autoclaved hastens the death of the animals; (3) that deficiency of protein and excess of starch play an important part in hastening the death of the animals; and (4) that life cannot be sustained in monkeys, of the species employed, for much longer than 100 days in the almost complete absence of accessory food factors of the 'B' class, other essential requisites of an adequate dietary having been provided.

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[1] See paragraphs 6 and 7 above.

Now, to my mind, the last fact has a great significance: it suggests that it is not so much with complete lack of 'B-vitamin' that we, as physicians, have to deal in practice, as with its subminimal supply. Complete deprivation of this accessory food factor means comparatively rapid death; subminimal supply means subnorimal function on the part of all organs and tissues and of the gastro-intestinal tract in particular. It requires a modicum of this substance to sustain life at all and such a subnormal existence constitutes in itself a state of disease. Indeed, experimental research provides abundant proof of this conception, for a rice imperfectly polished or imperfectly autoclaved, and containing traces only of this vitamine, will sustain life for longer periods than a rice devoid of vitamine, but in the end the inevitable dissolution is the same.

IV. LOSS OF BODY-WEIGHT

As the animals were exceedingly wild and difficult to handle they were weighed only at the beginning and at the end of the experiments. The average loss of weight in each category is shown in the table (p. 178).

From this table it is seen that the controls maintained a fairly constant level of weight; individuals, however, showed varying moderate losses or gains in weight (table, p. 176), the most notable being No. 16, which lost considerably. The relatively slight average loss of weight in the controls as a whole is attributable to the fact that sudden confinement of wild animals cannot fail to influence them unfavourably. The comparatively high level of health maintained by the controls is sufficient evidence of the appropriateness of their food supply. In no case did a control animal exhibit symptoms of gastro-intestinal disorder

Category and Number of Animals in each	*Average Weight Before Experiment (gm.)*	*Average Weight After Experiment (gm.)*	*Average Loss of Weight per kg. of Original Body-weight (gm.)*	*Average Days Under Experiment*	*Average Daily Loss of Weight, in gm. per kg. of Orginal Body-weight*
(i) Controls, 8	2,360	2,307	22	93·5	0·23
(ii) Autoclaved rice, 10	1,693	1,270	249	23·4	10·6
(iii) Autoclaved rice and butter, 4	2,217	1,655	253	15	16·8
(iv) Autoclaved food and onion, 6	1,748	1,190	320	71·1	4·5
(v) Autoclaved food, butter and onion, 5	2,422	1,710	294	65	4·5

apart from a tendency to constipation. During the earlier part of the experiment some of them developed jaundice. This symptom disappeared in the course of a few days on discontinuing the ground-nuts, limiting the dietary to milk and plantains, and adding to the milk a pinch of magnesium sulphate.

It will be noted that in all four categories of deficiently-fed animals the loss of weight ranged between 25 and 32 per cent, the most rapid loss of weight occurring in animals fed on autoclaved rice and butter. The table emphasizes the harmful influence exercised by the addition of the butter to a dietary excessively rich in starch and deficient in proteins and accessory food factors. It emphasizes also the important part played by an adequate supply of suitable protein in prolonging the life of the animals.

V. CLINICAL OBSERVATIONS

Monkeys in all four categories presented in general the same clinical features: progressive anaemia, asthenia, and gastro-intestinal disturbances. These, indeed, are to be regarded as the cardinal symptoms of the morbid state induced by the deficient dietaries. Some animals exhibited other clinical features which will be referred to under their appropriate heading. The essential difference in the four categories was the greater or lesser degree of rapidity with which these symptoms manifested themselves, and the greater or lesser delay in the inevitable issue—death.

The animals were unfortunately too wild to handle, so that it was found impracticable to make extended observations with regard to respiration and body-temperature. Such as were made towards the end of the experiment indicated that the temperature was usually subnormal and the pulse weaker and slower than in health.

(1) *Anaemia* made its appearance rapidly in animals fed on autoclaved rice, more slowly in those fed on autoclaved food. Judged by the intense pallor of the face, the degree of anaemia in animals fed on autoclaved food must have been pronounced. I was unable to undertake blood examinations.

(2) *Asthenia* was gradual in its onset in monkeys fed on autoclaved food, rapid in its onset in those fed on autoclaved rice. Towards the end of the experiment the degree of asthenia amongst animals in all categories was profound. Weakness of the limbs was, as a rule, well marked towards the end of the experiment in all animals. I was, however, unable to satisfy myself, by clinical methods of study, that this weakness was due to 'neuritis'. Examination of the peripheral nerves after treatment by Marchi's method revealed, however, a high proportion of degenerative change in animals fed on autoclaved food. No doubt, the weakness of the limbs was due in some part to these lesions. Monkeys exhibiting leg symptoms were observed to limp, one leg being kept flexed and held away from the ground, giving the impression of pain in the limb. It was noted also in more than one instance that the right leg would be so held on one day, the left on another. Towards the end of the experiment, when they were made to move about the floor of the laboratory, it was often observed that one limb tended to give way under the monkey's weight. This symptom applied to both upper and lower limbs so that animals so affected often toppled over on their sides and regained the erect position laboriously. Sometimes the lower limbs assumed a spread-eagle appearance and could only be drawn under the body with difficulty. As a rule, animals fed on autoclaved rice or on autoclaved rice with butter died before any noteworthy clinical symptoms other than intense weakness were observable in their limbs. The proportion of these cases exhibiting degenerative changes in the peripheral nerves was found to be small.

An appearance suggestive of wrist-drop was sometimes noted in animals fed on autoclaved food. The hands of healthy monkeys are often held in a dependent position, but while in health this position appeared to be one of choice, in the diseased animals it was often one of necessity. An animal, would be observed to interest itself in the capture of body-fleas, all movements to this end being carried out with the wrist in the 'wrist-drop' position. In this pursuit it seemed to be unaware that surprised the tips of the first finger and thumb were not in opposition, and to be when the object of its search was not found between them.

Two monkeys, fed on autoclaved food, devoted a great deal of their time, before they became too weak to do so, to the capture of flies which they ate greedily. One animal, especially skilful in this pursuit, survived for as long as 100 days on the autoclaved food-butter-onion dietary. No doubt they were aware of some want in the food and employed this device to remedy it.

(3) *Headache* appeared to be a fairly constant symptom, if one was justified in assuming its presence by the attitudes taken up by the animals: they were often observed to support the head in the hand as though in pain. Those fed on autoclaved food almost always presented towards the close of the experiment a dazed expression, suggestive of wonder or surprise at the feeble state in which they found themselves.

(4) *Gangrene* of the tail was met with in a number of cases.

(5) *Diminished sensibility* was undoubtedly present in the majority of animals in all four categories towards the end of the experiment. It was often noted, as regards the tail, that the animals seemed to be quite unaware of the fact that one had placed one's foot upon it. I have often tapped the tail sharply with a ruler from the tip to the root without the animal appearing to be aware of my action.

While, then, I am unable to say on clinical grounds that any of these animals suffered from 'polyneuritis', it was obvious that, in the autoclaved food class, the majority of them, during the later days of the experiments, exhibited a pronounced depression of functional capacity of the nervous system; this conclusion was confirmed by subsequent examination of the peripheral nerves.

(6) *Gastro-intestinal disorders*. These have been dealt with at length in another place in so far as they were observed to affect monkeys fed on (a) autoclaved rice, and (b) autoclaved rice and butter.[1] To this account the reader is referred. In character these disorders were the same in all four categories although differing in incidence or degree. It will suffice, therefore, to summarize the clinical observations under the heading in so far as they refer to the remaining two categories, i.e. (a) those fed on autoclaved food and onion, and (b) those fed on autoclaved food with butter and onion.

(7) *Loss of appetite* made its appearance much later in the two classes of animals fed on autoclaved food than in those of the two classes fed on autoclaved rice. Indeed, the appetite remained, as a rule, fairly good in the former up to within seven to ten days of the fatal issue.

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[1] **Numbers 73 and 74 in Bibliography.**

(8) *Vomiting* was observed in only one animal fed on autoclaved food and onion. In this case marked congestion of the stomach was found at autopsy, the mucous membrane of the pyloric half of the organ being especially congested and ecchymotic.

(9) *Diarrhoea.* This symptom was present in four out of six monkeys fed on autoclaved food and onion. Amoebae, but without ingested red-blood corpuscles, were present in two cases.

(10) *Dysentery.* This symptom was present in one animal fed on autoclaved food and onion, and in four fed on autoclaved food with butter and onion. Amoebae, having ingested red-blood corpuscles, were present in two cases.

Of eleven animals, therefore, the basis of whose dietary was autoclaved food, nine had either diarrhoea or dysentery. In eight of these colitis was a prominent feature at autopsy. It occasionally happened that in a given animal diarrhoea was present at some time during the earlier days of the experiment and dysentery during the later days. Thus, in monkey No. 21, fed throughout the course of the experiment on autoclaved rice plus onion, diarrhoea, which was blood-stained but without amoebae, made its appearance on the twenty-second day and persisted for several days. The symptom then cleared up only to reappear as a grave dysentery 39 days later. The dysentery persisted until the animal was killed on the sixty-seventh day of the experiment. No pathogenic amoebae were present.

(11) *Dropsy.* No clinical evidence of dropsy was met with in any of the four categories.

(12) *Disorders of the skin.* Disordered function of the skin was evidenced chiefly by the changes which occur in the hair. It became coarse and staring and showed a marked tendency to fall out. The skin was often rough and scaly, and in some cases a scaly eczematous condition was present. It seemed also that the skin was less sensitive than usual. A bleeding eczematous condition of the parts surrounding the anus was observed in two monkeys. The coarse staring coats of guinea-pigs, fed on a scorbutic dietary, and the ease with which the hair falls out will be familiar to all who have used guinea-pigs for 'scorbutic' experimental work.

VI. MORBID ANATOMICAL FINDINGS

The procedure adopted in the case of pigeons, described in detail in a previous communication,[1] was followed also in monkeys. They were, as a rule, autopsied immediately after death, and the heart's blood examined by aerobic methods of culture. All organs were weighed with the least possible delay after their removal from the body.

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[1] Number 67 in Bibliography.

1. *Haemic infections*

Haemic infections, as demonstrable by aerobic methods of culture, were present as follows:

Control animals (eight)	Nil
Autoclaved rice (ten)	4
Autoclaved rice and butter (four)	1
Autoclaved food and butter (six)	1
Autoclaved food, butter, and onion (five)	Nil

The organisms were mainly of two kinds, as determined by microscopical examination: small cocci and coliform bacilli; no attempt, however, was made to differentiate them.

These findings would appear to indicate that autoclaved food with onion, or with butter and onion, is less favourable to the occurrence of haemic infections than is a dietary composed mainly of carbohydrates and deficient in vitamines.

2. *Weights of Organs*

The weights of the organs, in gm. per kg. of original body-weight, in controls and in animals of all four categories, are shown in the accompanying table. Original body-weight was taken as the basis for these calculations since it appears to afford a fairer criterion of the degree of departure from health. When calculated against the final body-weight of the animals the results are, of course, much more marked.

From a study of this table, it will be seen that the organs group themselves into three classes:

(i) Those which increase in weight in all four categories: the adrenals and brain.

(ii) Those which decrease in weight in all four categories: the thymus, heart, sub-maximillary glands, pancreas, spleen, liver, lungs, thyroid and testicles.

(iii) Those which show an increase in weight in some categories and a decrease in others: the pituitary and kidneys.

Now although neither the increase in weight of an organ on the one hand, nor its decrease in weight on the other, can *per se* be regarded as conclusive evidence of increased or of diminished functional capacity,

Organs	*Controls* 8	*Autoclaved Rice* 10	*Autoclaved Rice and Butter* 4	*Autoclaved Food and Onion* 6	*Autoclaved Food, Butter and Onion* 5
Adrenals	0·190	0·352	0·293	0·258	0·266
Adrenaline	0·000301	0·000393			
		0·000264	0·000224		
Thyroid	0·083	0·081	0·073	0·069	0·070
Pituitary	0·014	0·015	0·015	0·016	0·0118
Testicles	0·257	0·216	0·218	0·208	0·254
Thymus	0·54	Traces only	Traces only	Traces only	Traces only
Sub-maxillary glands	1·01	0·80	0·70	0·82	0·78
Pancreas	1·36	1·14	0·95	1·22	1·07
Spleen	1·5	1·3	1·1	1·2	0·9
Liver	29·8	26·4	27·8	22·2	25·3
Heart	4·47	3·53	3·44	3·03	3·8
Kidneys	5·03	5·16	5·3	4·6	4·8
Brain	28·8	41·5	32·4	37·0	29·8
Lungs	6·03	5·5	4·9	5·1	5·2

nevertheless notable alterations in weight, when taken in conjunction with histological changes, are important indications of disordered functional capacity.

The extent to which the various organs were affected by the dietetic deficiencies may now be considered.

(i) THE SALIVARY GLANDS

These organs, as represented by the sub-maxillary glands, undergo some degree of atrophy in consequence of all the deficient dietaries employed. The atrophy was most marked in animals fed on autoclaved rice and butter; that is to say, in animals whose dietary was excessively rich in starch and fat and deficient in protein and accessory food factors of the 'B' and 'C' classes. It is notable that in each category the salivary glands may be more affected in one animal than in an other. It seems probable that impairment of function of these organs may be regarded as one result of dietetic deficiency, and that the process of digestion is thus impeded at its very onset.

(ii) THE STOMACH

Dilatation of the stomach was a very common consequence of the deficient diets. It was invariably present in animals the starchy components of whose food were in great excess over other essential constituents. It was less marked in animals fed on autoclaved food (see table,

p. 188). The mucous membrane of the stomach was frequently congested and ecchymotic, especially in the region of the pylorus. Shallow ulcers in this locality were occasionally encountered (table, p. 188). Deficiency of accessory food factors alone, other components of the food being supplied in adequate quantity, is capable of giving rise to these congestive changes in the stomach although less frequently than in the presence of an excess of starch in the dietary. It will be noted from a study of the table (p. 188) that in the former circumstances gastric catarrh was present in five out of eleven cases. A notable finding in the case of the monkey No. 32, fed on autoclaved food with butter and onion, was a small area of recently developed carcinoma of the pylorus visible only on microscopical examination of sections.

(iii) THE DUODENUM

Pronounced congestion of the duodenum was a frequent result of the imperfect dietaries employed in these experiments. The congestion was often so marked as to extend to the serous coat of the bowel (table, p. 188). Such duodenal catarrh has been found in animals whose dietary was deficient only in accessory food factors as well as in those in which the carbohydrate element of the food was excessive; its incidence in the latter was much higher than in the former (table, p. 188), being least marked in animals whose dietary was deficient only in the 'B-vitamin'. Ulcer of the duodenum has not been met with in monkeys although it has been observed in guinea-pigs on a scorbutic dietary.[1] Thinning of the muscular coats of the duodenum and necrotic changes in its mucous membrane were also frequent accompaniments of dietetic deficiencies, but, as a rule, only when there was great excess of starch in the dietary.

(iv) THE SMALL INTESTINE

There is a remarkable tendency to intussusceptions in this organ which appears to be due in some measure to the dietetic defects. It is notable in this connection that the increase in cases of intussusception amongst the ill-fed German population during the late war has been commented upon by German physicians.[2] The tendency to extensive intussusceptions was less marked in monkeys fed on autoclaved food than those fed on autoclaved rice. Small invaginations were as frequently encountered in the latter, but they were, as a rule, obviously agonal in origin. Great distension of the small bowel leading to ballooning of certain areas and to 'air-locks' (the cause of much discomfort in certain gastro-intestinal disorders in human beings) is a common manifestation of dietetic deficiency. It was especially notable in animals whose food was excessively rich in starch and was, no doubt, the result of acid-fermentation in the small bowel. Enteritis was frequently present, sometimes involving the whole of the small bowel, sometimes limited areas only. The congestion of the bowel may even extend to the serous coat. It is notable that in animals fed on autoclaved food the small bowel was very little affected as regards congestive changes (table, p. 188), and that in general it suffered much less than in animals whose dietary was excessively rich in starch. In butter-fed animals, whether receiving autoclaved rice or autoclaved food, a peculiar yellow-white tinge was frequently imparted to the whole gastro-intestinal tract.

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[1] Number 69 in Bibliography.

[2] Rubner, M., *J. Amer. med. Ass.*, 123, 168, 1919.

(v) THE COLON

Colitis is one of the most common and most constant results of dietetic deficiency. It was present in every case except one in three out of the four categories in monkeys. Its incidence, although high, was notably less in animals fed on autoclaved food, butter, and onion (table, p. 188). The colitis was frequently very extensive and small ulcers with adherent sloughs were often encountered in colons of animals fed on autoclaved food. In some cases it involved the whole colon from the caecum downwards, the serous coat being often ecchymotic. More commonly it was limited to the lower part of the great bowel, while occasionally a patchy colitis was present affecting limited areas, usually of the mid-colon. In one control animal (No. 16), a small area of the mid-colon was congested giving to the mucous membrane a rose-pink tinge, but without erosion of the mucous membrane or ecchymosis of the serous covering of the bowel. The animal was constipated and had suffered from jaundice. In no control animal was colitis present. Ballooning of the caecum and colon with atrophy of the longitudinal muscular bands and loss of the normal puckerings of the great bowel were common appearances in all categories. These appearances are suggestive of impairment of its neuro-muscular control. It may here be noted that a diffuse, apparently cancerous, infiltration of the submucous coats of the lower end of the great bowel was found in one monkey fed on autoclaved food, butter, and onion. The bowel wall was at this area much thickened and tough to the scissors. The mucous surface presented the appearances seen in granular ophthalmia. On histological examination occasional fine epithelial projections into the submucous coat were noted, as well as groups of epithelial cells scattered throughout a fibrous infiltration of the submucous coat.

(vi) THE PANCREAS

Varying degrees of atrophy of the pancreas were constant consequences of the deficient and ill-balanced dietaries. In each of the four categories some animals were more affected in this regard than others. The atrophy was most marked when the diet was deficient in the 'B' and 'C' classes of vitamines and at the same time excessively rich in fats and in starch as well as poor in protein (table, p. 178). It was notable also that the atrophy was very considerable in animals whose dietary, while excessively rich in fats, was deficient only in 'B-vitamine'. This effect of excess of fat in increasing the degree of atrophy of the pancreas has been recorded also in pigeons.[1] It is difficult to resist the conclusion that an excessive fat intake, in the presence of vitaminic deficiency, is responsible for the more pronounced atrophic changes in the pancreas in these circumstances. Although anticipating a more complete account of the histo-pathology of the pancreas,[2] to be published at a later date, it may here be said that the histological changes in this organ were as indefinite in monkeys as they were in pigeons.[3] Apart from a diminution in size and shrunken appearance of the alveolar cells, and their less constant exhibition of the characteristic darkly-staining outer and lightly-staining inner zone, I have been unable definitely to detect any gross histological change with this exception; the alveolar cells in the atrophic organs were not found to exhibit in the same degree that loading with granular contents which is characteristic of the cell before secretion, and indicative of healthy functional activity. I have examined serial sections of the pancreas from all thirty-three monkeys employed in these experiments, but pancreatitis was never encountered. Occasionally small haemorrhages into the organ were present. To the naked eye the pancreas was usually pale in colour and of a consistency softer than in health. Although I cannot give a more definite account of the histological changes in the atrophic organ, the impression left by their study is that the function of the pancreas was in general considerably impaired. I have found no marked changes in the islets of Langerhans; it seems probable that these findings, viz.: (a) atrophy of the pancreas as estimated by weight, (b) its greater atrophy when the diet is deficient in 'B-vitamine' and protein and excessively rich in fats and starch, and (c) the histological appearances suggestive of diminished functional capacity may have an important bearing on the genesis of diabetes in Bengalis. A dietary of autoclaved rice and butter, such as those monkeys received whose pancreas was the most atrophic, is similar in many respects to that commonly used by the diabetic Bengali. If to such a dietary an excessive sugar intake were added, its similarity would be the more marked. My findings with respect to the pancreas and the gastro-intestinal tract appear to be complementary to those of Colonel McCay and his colleagues whose work on the subject of diabetes was published in the April 1919 number of this journal.[1]

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[1] Number 68 in Bibliography.

[2] This could not be done as R. McC. was invalided to England shortly after this paper was written.

[3] Number 71 in Bibliography.

Their conclusions as regards the gastro-intestinal changes, attributable to the highly carbonaceous dietary of the Bengali, find ample confirmation in the facts I have recorded. In my monkeys the urine was frequently aspirated from a full bladder at autopsy; its examination for sugar invariably yielded negative results. Blood-sugar estimations were made in a number of animals fed on autoclaved food, butter, and onions, but in no case was hyper-glycaemia encountered. My attention was unfortunately not directed to this aspect of the research until the majority of the monkeys had succumbed. The changes induced in the adrenal glands by dietetic deficiency may not be without influence in regard to the genesis of diabetes.

(vii) THE LIVER

It will be noted from the table (p. 178) that in all categories the weight of the liver per kg. of body-weight was considerably below that of health. This was especially notable in animals fed on autoclaved food and onion. But it is difficult in animals of this category, as well as in animals fed exclusively on autoclaved rice, to form a just appreciation of the extent of this atrophy since in both of these categories the animals were, as judged by weight, considerably younger than the controls. One is not aware, therefore, of the normal weight of the liver per kg. in young animals. No such difficulty arises, however, in the case of monkeys fed on autoclaved rice and butter, nor in that of animals fed on autoclaved food, butter, and onion. Between these a just comparison is possible since the animals in these categories, as well as the control animals, were adults. It may be concluded, then, that lack of 'B-vitamine' alone can cause a notable degree of atrophy of the liver. It will be observed that in the two main categories—(a) those fed on autoclaved rice, and (b) those fed on autoclaved food—the atrophy was not so great when butter was added to the dietary. This result has previously been recorded for pigeons.[2]

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[1] McCay, D. *et al.*, *Indian J. med. Res.*, 6, 485–508, 1919.

[2] Number 68 in Bibliography.

Toxic absorption from the diseased gastro-intestinal tract will arise with the more ease in proportion as the liver is impaired in its function by the deficient dietary. The gall bladder was frequently observed to be distended in these animals.

For purposes of comparison I have prepared the following table showing the lesions of the digestive organs encountered at autopsy in monkeys fed on the various deficient dietaries:

Lesions of the digestive organs found in monkeys fed on the various deficient dietaries.

Lesions	*Controls*	*Auto-claved Rice*	*Auto-claved Rice and Butter*	*Auto-claved Food and Onion*	*Auto-claved Food, Onion, and Butter*
Number of Animals	8	10	4	6	5
Atrophy of sub-maxillary glands[1]	Nil	6	4	5	2
Dilatation of stomach	Nil	10	4	4	2
Gastric catarrh	1(No. 16)	7	3	3	2
Ulcer of pylorus	Nil	Nil	1	2	Nil
Carcinoma of pylorus	Nil	Nil	Nil	Nil	1
Duodenal catarrh	Nil	7	3	2	1
Sub-serous ecchymosis of duodenum	Nil	5	1	1	1
Duodenal ulcer	Nil	Nil	Nil	Nil	Nil
Congestive changes in jejunum	Nil	8	1	1	1
Congestive changes in ileum	Nil	7	2	Nil	Nil
Sub-serous ecchymosis of jejunum	Nil	5	Nil	1	Nil
Sub-serous ecchymosis of ileum	Nil	3	1	Nil	Nil
Ballooning of small bowel	1(No. 16)	6	4	2	2
Thinning of bowel walls	1(No. 16)	10	4	2	4
Intussesception	Nil	6	4	5	3
Colitis	Nil	10	3	6	2
Sub-serous ecchymosis of whole colon	Nil	2	Nil	1	1
Sub-serous ecchymosis of lower colon only	Nil	5	1	3	2
Ballooning of colon	1(No. 16)	6	3	4	3
Atrophy of colon walls	Nil	10	4	3	4
Enlargement of mesenteric glands	1(No. 16)	10	4	6	4
Atrophy of omentum	Nil	10	4	6	5
Atrophy of pancreas[2]	Nil	6	2	4	2

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[1] Cases are noted as having atrophic sub-maxillary glands and pancreas when the weight of these organs was less than the lightest amongst controls.

[2] Intussusceptions are noted in every case in which they were present. The great majority of them were agonal in character. All were such in animals fed on autoclaved food, butter and onion; all but one were such in animals fed on autoclaved food and onion, while in other categories a considerable proportion, as judged by their size and appearance, had probably occurred some time prior to death.

The table brings into prominence the importance of excess of starch in accentuating the changes initiated by the dietetic deficiency. It would appear that it is to the excessive starchy component of the food that a considerable proportion of the disorder in the stomach and small bowel is attributable. It will be noted that while the stomach and the small intestine are adversely influenced by the excess of starch, the colon appears to suffer equally whether the deficient dietary is excessively rich in starch or not. It is notable also with what constancy the omentum is devoid of fat in all categories. It seems to me not unlikely that the loss of the protective layer of omental fat is calculated to increase the susceptibility of the intestines to such influences as chill, enveloped as they are in health by the fat-laden omentum. Again the great constancy of enlargement, discolouration and infection of the mesenteric glands introduces the question of 'intestinal toxaemia'. These glands have yielded growths of coliform organisms and cocci by aerobic methods of culture. The absorption of poisonous products through the intestinal mucosa is greatly facilitated by an unhealthy state of its epithelium, and it is clear that deficiency of accessory food factors, especially when associated with deficiency of proteins and an excessive starch intake, leads to malnutrition, necrosis, and desquamation of the gastro-intestinal epithelium. The toxic products derived from the intestinal contents, and from the desquamated cells themselves, would in these circumstances, find no difficulty in reaching the blood-stream in large amounts. Dietetic deficiency may then be regarded as a common cause of intestinal toxaemia, for such degrees of injury to the gastro-intestinal mucosa as may be necessary to admit of toxaemia from the bowels are readily produced by dietetic deficiencies. Then, too, the liver—that sentinel of the gastro-intestinal tract against toxaemia—suffers markedly in consequence of the deficient dietaries, and it seems probable that toxic products which in health are readily destroyed by it may in circumstances of dietetic deficiency be allowed to pass in considerable quantity.

(viii) THE ADRENALS

All classes of deficient dietary hitherto employed, whether in pigeons, guinea-pigs or monkeys, give rise to enlargement of the adrenal glands. The adrenaline content of the enlarged organs differs greatly with different classes of deficient and ill-balanced dietaries. It is dependent also to a very large extent on the presence or absence of haemic infections: when haemic infections were present the adrenaline content per gm. of gland was invariably low. I have previously reported: (a) a low adrenaline content in consequence of a scorbutic dietary in guinea-pigs,

(b) a high adrenaline content in consequence of an exclusive dietary of autoclaved rice in pigeons, (c) a low adrenaline content in pigeons (with certain exceptions) fed on autoclaved rice plus butter. All these observations have reference only to animals in which no haemic infection was demonstrated at autopsy by aerobic methods of culture. In the present experiments the adrenaline content was high in monkeys fed exclusively on autoclaved rice whose blood was found to be sterile at the time of death, 0·000393 gm. per kg. of original body-weight; low in monkeys fed on autoclaved rice and butter, 0·000224 gm. per kg. of original body-weight (table, p. 188), thus confirming previous observations in pigeons. It was low also in monkeys fed on autoclaved food whether with or without butter. Although it is not possible at present to appreciate the true significance of these results, it is obvious that the nature of an animal's food has a profound influence on the adrenaline content of the adrenal glands.

Oedema. In previous communications[1,2,3] I have drawn attention to the intimate association of adrenal hypertrophy with oedema. In the present experiments evidences of oedema were scanty:

These were as follows:

(a) Monkey No. 7 fed on autoclaved rice: 1 c.c. of fluid in the pericardium.
(b) Monkey No. 9 fed on autoclaved food with onion: 4 drops of fluid in the pericardium.
(c) Monkey No. 33 fed on autoclaved food with onion and butter: ½ c.c. of fluid in the pericardium.
(d) Monkey No. 34 fed on autoclaved food, butter and onion: 5 c.c. of fluid in the abdominal cavity.

These findings are too scanty to admit of any conclusions being drawn with regard to them, especially so as 3 drops of fluid were present in the pericardial sac of one control animal.

(ix) THE PITUITARY

It will be observed that the pituitary of monkeys fed on autoclaved rice, on autoclaved rice and butter, and on autoclaved food and onion, increased in weight. Thus is the finding previously reported in pigeons confirmed.[1,2] It is found also on analysing the figures further that the average weight of the pituitary per kg. of body-weight in healthy male monkeys of this species is 0·0133 gm., in healthy females 0·0152 gm. In health the organ is thus considerably heavier in females than in

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[1] Number 67 in Bibliography.
[2] Number 68 in Bibliography.
[3] Number 87 in Bibliography.

males, a finding which confirms previous observations in pigeons.[1] While, however, the pituitary enlarges in male monkeys, fed on autoclaved rice, to 0·015 gm. per kg. of original body-weight, in females similarly fed it does not enlarge, being but 0·014 gm.; a result which confirms that previously recorded for pigeons.[2] In these experiments a notable finding with regard to the pituitary was the marked drop in weight of this organ in monkeys fed on autoclaved rice with butter and onions. I have at present no explanations to offer of this observation.

(x) THE THYMUS

In monkeys, as in pigeons,[1,2] the thymus atrophies sometimes to the point of almost complete disappearance in consequence of an autoclaved rice dietary. The same is true with regard to autoclaved food. In one young monkey in the former category the thymus weighed 0·15 gm. per kg. of original body-weight as compared with an average of 0·54 gm. in health. In another baby monkey in the autoclaved food category, the thymus weighed but 0·08 gm. per kg. of original body-weight. In most other cases the organ existed in traces only.

(xi) THE TESTICLES

The degree of atrophy of the testicles observed in monkeys in consequence of the deficient dietaries is very much less marked than that found in pigeons. The atrophy of the testicles in monkeys was most marked in those fed on autoclaved food with onions; that is to say, in those whose food was lacking in the 'A' as well as the 'B' factor. In animals from whose dietary the latter vitamine alone was wanting, the changes in the testicles, as indicated by weight, were trifling.

(xii) THE FEMALE REPRODUCTIVE ORGANS

These organs were not weighed in monkeys. To the naked eye they appeared small and atrophic, the uterus being commonly flattened antero-posteriorly and having lost in great measure its plump, pear-shaped appearance. It was often congested under its serous covering, as also was the ovary. It will be remembered that during the late war 'amenorrhoea' was a frequent symptom of food deficiency.

(xiii) THE SPLEEN

Both the spleen and the testicles present in regard to their degree of atrophy a remarkable contrast in pigeons and in monkeys. The lesser atrophy of these organs in monkeys is one of the outstanding differ-

[1] Number 67 in Bibliography.

[2] Number 68 in Bibliography.

ences in the response of the two species to the action of food deficiencies. It is notable that the atrophy of the spleen is more considerable in butter-fed animals—a finding which has previously been recorded in pigeons.

(xiv) THE HEART

It is a remarkable fact that in no case was hypertrophy of the heart, comparable to that found in human beri-beri, observed in monkeys. In all categories the atrophy of the heart was pronounced, being most marked in animals fed on autoclaved food and onions.

(xv) THE KIDNEYS

The gravimetric findings with regard to the kidneys are peculiar. In monkeys the basis of whose dietary was autoclaved rice, there was a slight tendency to increase in weight of these organs; in those the basis of whose dietary was autoclaved food there was a slight tendency to decrease in weight (table, p. 178). The urine was examined at autopsy in a number of cases but with negative result in so far as the presence of albumen was concerned. The naked-eye appearance of the kidneys presented, as a rule, no more worthy features; in some cases, however, the organs were noted to have been anaemic.

(xvi) THE THYROIDS

In monkeys, as in pigeons,[1,2] the degree of atrophy of the thyroid is not great. It is notable that the addition of butter to the dietary of autoclaved rice increased the degree of the atrophy; for whereas the average weight of the thyroid in monkeys fed exclusively on autoclaved rice approximated closely to that of health, being 0·081 gm. as compared with 0·088 gm., in animals which received butter in addition to the rice it was but 0·073 gm. I have recorded a similar finding in pigeons.[1,2]

(xvii) THE LUNGS

The loss of weight of the lungs, in all four categories, is noteworthy, more especially as I found, in pigeons fed on autoclaved rice, butter and onions, a marked increase in weight of the lungs.[2]

(xviii) THE BRAIN

With regard to no organ has the gravimetric method of study followed in these experiments yielded more remarkable results than in the case of the brain. Its superficial vessels were often much engorged and

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[1] Number 67 in Bibliography.
[2] Number 68 in Bibliography.

in some animals, fed on autoclaved food, onion, and butter, a decided increase in cerebro-spinal fluid was observed. The weights of this organ in the four categories are not strictly comparable since the weight of the brain varies widely at different age periods in man, and no doubt varies in like manner in monkeys. The controls are, however, comparable with animals fed on autoclaved rice and butter, and with those fed on autoclaved food, butter and onion. It will be noted that in the last two categories the average weight of the brain per kg. of original body-weight is higher than in controls, being markedly so when the dietary is excessively rich in starch as well as in butter—a finding which confirms that previously recorded in pigeons.[1] In control pigeons the weight of the brain per kg. of body-weight was 6·262 gm., while in those fed on autoclaved rice, butter and onion, it was 7·212 gm. per kg. of original body-weight, or about one-seventh part heavier than in health. In monkeys the corresponding weights are, for health 28·8 gm., and for the diseased state 32·4 gm., or again about one-seventh part heavier than in health. It appears to be more than a coincidence that in both species the addition of butter to an autoclaved rice dietary should cause an increase in weight of the brain of one-seventh its normal weight. It may be taken, then, as established that the weight of the brain is markedly increased by a dietary excessively rich in starch and fats and deficient in proteins and accessory factors of the 'B' class. These findings indicate that the brain is capable of considerable variations in weight, and it may be presumed also of bulk dependent upon the composition of the food. The importance of this observation with respect to the occurrence of headaches, mental confusion, lack of concentration, and other evidences of mental disorder in man would appear to be considerable. The influence of diet on the causation of mental disease has been emphasized by Dr. Charles Mercier[2] as a result of his clinical observations. The observations here recorded appear to provide experimental proof of his contentions: he found that headache was a frequent consequence of a dietary excessively rich in fats and starch and that deficiency of meat was a potent cause of mental confusion. A rate of between 94 to 95 per cent of recovery, or very great improvement, occurred in his practice amongst those exhibiting these evidences of mental disorder whose dietary was corrected.

(xix) THE NERVES

For diagnostic purposes portions of the femoral nerve or of its branches in the thigh were removed in all thirty-three animals. These were treated by Marchi and Algeri's method for the demonstration of fatty degeneration of the myelin-sheath. The familiar appearance of Wallerian degeneration were taken as the criterion of degenerative change. In addition to these appearances the staining of the myelin-sheath of some fibres was of a more diffuse and patchy character. As, however, such appearances are capable of being produced in nerves from apparently healthy animals—in consequence, it may be, of stretching at the time of removal—no nerve was classed as degenerated unless it contained some fibres exhibiting the characteristic Wallerian appearances. Minute precautions were taken at the time of autopsy to avoid injury to the portions of nerve removed for examination. While, therefore, my estimate of the degree of degenerative change attributable to the various deficient dietaries may be too low, it is certainly not too high. The incidence of nerve-fibre degeneration in the peripheral nerves of the thirty-three animals was as follows: controls, *nil*; autoclaved rice, two; autoclaved rice and butter, one; autoclaved food and onion, four; autoclaved food, butter and onion, two. It would seem from these results that the incidence of nerve-fibre degeneration is largely a question of length of exposure to the dietetic deficiency. While the high percentage of cases exhibiting degenerative changes amongst animals fed on autoclaved food was, no doubt, due to deficiency of 'B-vitamine', it is to be noted that animals receiving butter in addition to autoclaved food showed a lesser incidence of nerve-fibre degeneration than those receiving autoclaved food and onion only. The number of degenerated fibres varied in each case within fairly wide limits. In monkey No. 29, fed on autoclaved rice and butter, two fibres only were encountered which presented typical Wallerian degeneration. In other cases the proportion was considerably higher: a rough estimate of the number of fibres involved being about 5 to 10 per cent. These findings indicate that the weakness of the limbs, referred to in the section dealing with clinical observations, is to be attributed, in part at least, to degenerative changes in the nervous system. The Wallerian character of the degeneration would appear to point to degenerative change in certain cells of the central nervous system.

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[1] Number 68 in Bibliography.

[2] Mercier, C., *Lancet*, i, 510–13, 561–5, 1916.

VII. SUMMARY OF RESULTS

(1) Monkeys fed exclusively on rice, autoclaved at a temperature of 130° C. for 1½ hours, died in an average period of 23·4 days.

(2) Monkeys fed on rice similarly autoclaved, to which fresh butter was added, died in an average period of 15 days. The addition of butter to the dietary (excessively rich in starch and deficient in vitamines and

protein) hastened the death of animals. A similar finding has previously been recorded in the case of pigeons.[1]

(3) Monkeys, the basis of whose dietary was autoclaved food, survived much longer than those the basis of whose dietary was autoclaved rice: an average of 70 days as compared with an average of 20 days. The more liberal provision of protein and the more perfect balance of the food, with respect to protein and carbohydrates, prolonged the life of the animals in the former category.

(4) Monkeys (*macacus sinicus*) cannot sustain life for periods much longer than 100 days on a dietary which is devoid of accessory food factors of the 'B' class. Lack of this factor is a fundamental cause of the animals' dissolution; deficiency of protein, excess of starch, and excess of fat in the absence of 'B-vitamine' contribute to this dissolution.

(5) The total loss of weight in monkeys of all four categories was from 25 to 32 per cent of the original weight of the animals; the greatest loss being in those fed on autoclaved food and onion, that is, in those which survived the longest time. Those to whose dietary of autoclaved rice butter was added lost weight more rapidly than those receiving no butter.

(6) The chief clinical evidences of disease due to the deficient dietaries were progressive anaemia, and asthenia, loss of appetite, diarrhoea, dysentery, diminished sensibility, weakness of the limbs, headache, impaired nutrition of the skin, subnormal temperature, and enfeebled heart's action. Symptoms referable to the nervous system were less prominent and appeared later than those referable to the digestive system; they were for the most part obscured by the profound asthenia.

(7) The symptoms were similar in all four categories, but manifested themselves later in monkeys whose food was more perfectly balanced with respect to protein and carbohydrates.

(8) Symptoms referable to the digestive system were on the whole less common in monkeys whose food was more perfectly balanced with respect to protein and carbohydrates. Nevertheless, gastritis and colitis were frequent clinical features in these animals.

(9) Dropsy was not present in any of the monkeys fed on the deficient dietaries.

(10) Haemic infections, as determined by aerobic culture of the heart's blood at autopsy, were commonly present in monkeys whose food was excessively rich in starch and deficient in protein and vitamines.

(11) All classes of deficient dietaries caused in monkeys an increase in weight of the adrenal glands. This increase was more marked in those fed exclusively on autoclaved rice and was associated with an increase

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[1] Number 68 in Bibliography.

in the adrenaline content of the glands, provided no haemic infecti was present. No increase in the adrenaline content of the adren glands occurred in monkeys to whose dietary of autoclaved rice butt was added. Similar findings have previously been recorded in pigeon

No increase in the adrenaline content of the adrenal glands w found in monkeys whose deficient dietaries were more perfectly balance with respect to proteins and carbohydrates. The adrenaline content the adrenal glands was below the average of health in monkeys presen ing haemic infections.

(12) The left adrenal was one-seventh part heavier than the right p kg. of body-weight in healthy monkeys. This proportion was mai tained when the animals were fed on autoclaved rice or on autoclave food. When, however, butter was added to the autoclaved rice or to th autoclaved food the difference in weight between the left and the rig adrenal was more marked; the left adrenal was then one-fourth to on fifth part heavier than the right.

(13) The deficient dietaries gave rise in all categories to an increase weight of the brain. When similarity in the age of the monkeys render the findings in the different categories comparable it was noted that t increase in weight of the brain was more marked in those whose fo was excessively rich in butter and starch and at the same time deficie in protein and vitamine. A similar finding has previously been record in pigeons. The increase in weight of the brain in these circumstanc amounts in monkeys to approximately one-seventh part of its norm average weight per kg. of original body-weight; it amounts also pigeons to approximately one-seventh part of the normal average p kg. of original body-weight. It is suggested that this finding m account for the headache and other symptoms observed in certain cas of mental disorder in the human subject.

(14) Three classes of deficient dietaries, viz. (a) autoclaved rice, (autoclaved rice and butter, and (c) autoclaved food and onion, caus in monkeys an increase in the weight of the pituitary body. This org was found to be decreased in weight in monkeys fed on autoclaved fo butter and onion. Similar findings have been recorded in the case pigeons fed on the first two classes of deficient dietaries above-mentione

The pituitary gland was heavier per kg. of body-weight in female th in male control monkeys. A similar finding has been recorded in the ca of pigeons. The pituitary gland increased in weight in male but not female monkeys in consequence of an exclusive diet of autoclaved ric a similar finding has been recorded in the case of pigeons.

(15) Atrophy of all other organs—the thyroid, the reproducti organs, the thymus, the submaxillary gland, the pancreas, the spi

the liver, the heart, the kidneys, the lungs—occurred in consequence of the deficient dietaries. The kidneys, however, showed a diminution in weight only in those animals the basis of whose dietary was autoclaved food. The atrophy of the testicle was also slight in monkeys fed on autoclaved food, butter, and onion.

(16) The atrophy of the pancreas, the thyroid, the spleen, and the heart was more marked in monkeys to whose deficient dietary of autoclaved rice butter was added. A similar finding has previously been reported in pigeons. The atrophy of the submaxillary gland was likewise more marked in monkeys whose deficient dietaries were excessively rich in butter.

(17) The decrease in weight of the liver was not so marked in monkeys to whose dietary of autoclaved rice or of autoclaved food butter was added. A similar finding has been recorded in the case of pigeons fed on autoclaved rice, butter, and onion.

(18) In addition to the enlargement or atrophy of the organs above referred to the main pathological states observed in monkeys at autopsy were dilatation of the stomach, gastritis, duodenitis, enteritis, ballooning of the small intestine, intussusception, colitis, atrophy of the muscular coats of the bowel, complete loss of fat from the omentum, and enlargement of the abdominal lymphatic glands.

(19) The excessive starch element, in the absence of protein and vitamins, appeared to be largely responsible for the great dilatation of the stomach, the ballooning of the bowel and the 'air-locks' in the intestine. The stomach and the small bowel were less affected in monkeys whose food was more perfectly balanced with respect to protein and carbohydrates. In general, the gastro-intestinal tract was not so frequently nor so extensively diseased in animals fed on autoclaved food, butter, and onion, although both gastritis and colitis were present in 40 per cent of these animals.

(20) In all categories atrophy of the heart occurred; it was less marked in animals fed on autoclaved food, butter, and onion. In no case was hypertrophy of the heart encountered. Slight hydropericardium occurred in a small percentage of cases.

(21) The reproductive organs atrophied to a considerable extent in both sexes, but the atrophy was much less marked than that previously found in pigeons in like circumstances. Sub-serous congestion of the uterus and ovaries was frequently present.

(22) The atrophy of the spleen was less marked in monkeys than in pigeons similarly fed.

(23) The weight of the lungs decreased in monkeys in all categories, thus contrasting markedly with pigeons in which an increase in weight

of these organs was noted to result from a dietary of autoclaved rice, butter and onion.

(24) Post-mortem evidences of oedema were very scanty in all four categories.

(25) Degenerative changes were present in the femoral nerves as follows: controls, nil; autoclaved rice, two; autoclaved rice and butter, one; autoclaved food and onion, four; autoclaved food, butter and onion, two.

VIII. CONCLUSIONS

(1) Dietaries which are deficient in vitamines and in protein, and at the same time excessively rich in starch or in fat or in both, are potent sources of disease and especially of gastro-intestinal disease.

(2) An excess of fat, in association with deficiency of 'B-vitamine' and protein and superabundance of starch, is peculiarly harmful to the organism.

(3) Certain dietetic deficiencies favour the invasion of the blood and tissues by bacteria, especially when deficiency of vitamines and protein is associated with an excessive intake of starch.

(4) Since life cannot be sustained in *macacus sinicus* for much longer than 100 days on a dietary almost wholly devoid of 'B-vitamine', it would appear that complete absence of this vitamine from the food of human beings is of less practical importance, from the point of view of disease production, than is its subminimal supply. Complete deprivation of 'B-vitamine', especially in the presence of imperfect balance in other essential requisites of the food, will lead to rapid dissolution and death; subminimal supply of this vitamine will lead, in like circumstances, to slow dissolution and disease.

(5) It is thought that the findings recorded in this paper may afford some explanation of the genesis of that great mass of ill-defined gastro-intestinal disorder and vague ill health which forms so high a proportion of human ailments at the present day.

On the Occurrence of Recently Developed Cancer of the Stomach in a Monkey Fed on Food Deficient in Vitamines[1]

In the present issue of this Journal I have recorded the effects on monkeys of certain deficient dietaries. The occurrence of a recently developed cancer of the pylorus in one of these animals may have been a fortuitous circumstance unconnected with the dietetic defect. On the other hand, it is possible that the malignant growth may have been connected in its origin with the deficiency of certain food factors; in this event the observation would assume a high importance.

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[1] Extract from number 79 in Bibliography.

The facts of the case are these: the animal was an adult female monkey of the species *macacus sinicus*. It was captured in the local jungles some few days prior to its arrival in my laboratory. It was very vigorous and appeared to be in perfect health. It weighed 2,400 gm. It was fed for the first ten days of the experiment on rice and butter—120 gm. of the former and 15 gm. of the latter. The rice was autoclaved at a temperature of 130° C. for one hour and a half. Of this food the animal ate freely at first, more sparingly towards the end of the ten days. On the eleventh day the diet was changed to 60 gm. of rice, 60 gm. of wheaten bread, 120 gm. of milk, 10 gm. of ground-nuts, 15 gm. of fresh butter, and 5 gm. of onion. The rice, bread, milk and ground-nuts were autoclaved at a temperature of 130° C. for one hour and a half in order to destroy completely their content of B-vitamine. The butter and onions were given fresh. The food thus contained an adequate supply of 'A' and 'C' vitamines but was deficient in 'B' vitamines.

The animal survived this dietetic régime for fifty-one days. Its weight at death was 1,950 gm., a loss of 450 gm. It exhibited, during the course of the experiment, the following symptoms: diarrhoea, progressive anaemia, asthenia, and, during the last nine days, severe dysentery. The animal was autopsied immediately after death.

The stomach was greatly dilated but presented no other naked-eye evidences of disease. Following my laboratory routine in such cases, a portion of the stomach, one centimetre square, embracing all coats of the organ, was removed from the neighbourhood of the pylorus for sectioning. The tissue was fixed in Zenker's fluid, embedded in paraffin, sectioned and stained with haematoxylin. Three such specimens were examined. An obvious carcinoma was present. The surface of the growth was flush with the mucous surface of the stomach and exhibited no excrescences towards the cavity of the viscus. Numerous epithelial down-growths projected into the submucous coat. This coat appeared somewhat thickened beneath the growth. The down-growths had not penetrated deeply into the submucosa; the vertical area occupied by them scarcely exceeded that which would have been occupied by the glandular elements they replaced. The cells near the advancing edge of the growth stained well, their staining capacity gradually diminishing towards the mucous surface of the stomach. The older cells were of hyaline appearance, their nuclei having disappeared or having failed to retain the stain. The two remaining specimens were not in series with the first; they showed but occasional microscopic nodules of the carcinoma. Further sections taken from the same block showed no growth.

The discovery of this area of carcinoma was largely a matter of chance since there was no naked-eye evidence of its presence. Such early cancers may very easily be missed unless microscopical search is made for them throughout serial sections of the organ. It may be that this carcinoma was the only case of cancer of the stomach in my series of monkeys; on the other hand, it is quite possible that I may have missed others. That the carcinoma was of recent origin seems probable since the area of the pyloric mucosa involved by it was of very small size. Its superficial area in a transverse direction did not, in the sections examined, exceed 3½ fields of the low power of the microscope. I have no evidence as to its extent in a longitudinal direction. The growth barely extended in point of depth beyond the limits of the mucous membrane, its invasion of the submucous coat being but slight. The deeper coats of the stomach were unaffected and no puckering or contraction of the walls of the viscus had occurred. For these reasons I am inclined to think that the carcinoma was of recent origin and that in all probability it developed during the fifty-one days of the experiment. However this may be, the experience would seem to justify the prosecution of an inquiry into the possible influence of vitaminic deficiency in favouring the onset of cancer of the stomach.

CHAPTER IV

Researches on Beri-beri

The Relationship of Rice to Beri-beri in India[1]

I. INTRODUCTION

Present-day views as to the association of tropical beri-beri with the too exclusive use of a rice diet may be summarized as follows:

(1) When decorticated rice is used as the main staple of diet for any length of time beri-beri appears.

(2) Outbreaks of the disease disappear when whole or under-milled rice is substituted for decorticated rice.

(3) Beri-beri never appears when under-milled rice only is used.

(4) Beri-beri does not occur when parboiled rice is eaten.

(5) A rice which contains over 0·4 per cent of phosphorus pentoxide (P_2O_5) will not cause beri-beri, while one with less than that amount is unsafe if rice forms the principle article of diet.

(6) The incidence of beri-beri depends on the treatment to which rice is subjected before consumption.

(7) Beri-beri is directly caused by deficiency of a certain vitamin or vitamins in the diet.

Although these views are generally held by those who have devoted attention to this protean malady, certain results reached in the course of the 'Deficiency Diseases Inquiry' have raised doubts in regard to them—doubts which have been enhanced by epidemiological studies. It was found, for instance, that although rice is the staple article of diet of many millions of the people of India, beri-beri is not widely distributed over this country. It is limited, as an endemic, to the coastal areas of the six districts forming the North-east Coast Division of the Madras Presidency ('the Northern Circars')—Ganjam, Vizagapatam, Godavari, Kistna, Guntur and Nellore, to a few circumscribed areas of Bengal and Assam, to the coast of Burma, and to the valleys of the Irrawaddy and Salween rivers in that province. Isolated cases, or even small outbreaks, occur from time to time in other parts of the Indian peninsula; but these are usually confined to troops (British or Indian), to the crews of the ships touching at Indian ports, to prisoners in jails, to certain Chinese communities, and to former residents of endemic areas who have migrated to other parts of India. Emigrants from these areas are much more subject to the malady than the rice-eating inhabitants of non-endemic areas. Thus, Madrassi troops provided approximately 90 per cent of the total cases of beri-beri in the Native Army during the years 1900–20, although Madrassis formed no more than a sixth part of its total strength. Further, in the great endemic centre of this disease in the Madras Presidency, the malady is by no means most common amongst those who restrict themselves most rigidly to the use of rice.

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[1] Extract from number 4 in List of Books and Memoirs.

These epidemiological observations had been made when a copy of the little-known work of Malcolmson, entitled *A Practical Essay on the the History and Treatment of Beri-beri*, published in 1835, was obtained with difficulty. It was learned from it that beri-beri 'prevailed extensively' in the North-east Coast Division of the Madras Presidency a century ago; and that emigrants from this district were peculiarly prone to attacks of the malady in their adopted homes. Beri-beri was, therefore, common in its present endemic haunts long before the machine-milling of rice was introduced into India, and at a time when the home-pounding of rice and the use of unpolished rice were universal customs. Our more recent epidemiological studies confirm the work of Malcolmson and indicate that beri-beri still prevails extensively in these areas of the Madras Presidency while outside them it is rare in this Presidency as in other parts of the Indian Peninsula. The home-pounding of rice and the use of unpolished rice are still the common practices in country districts of these endemic areas, and rice so prepared is still associated with beri-beri in them although less frequently than when milled rice is used. Despite the present profusion of rice mills the disease appears to have extended its endemic borders but little, if at all, during the past eighty-eight years. Nor have examples of its association with the use of parboiled rice been wanting in endemic areas, although none have been met with in non-endemic areas. These are facts which hardly accord with present-day views. If we add to them the knowledge, derived from experiments on animals, that vitamin-B deficiency, when its effects are uncomplicated by those of other agents, causes neither the complete clinical nor the complete pathological picture of beri-beri, it must be admitted that there is reason for the doubts which have arisen as to the strict applicability to India of present-day views in regard to the association of a rice diet with beri-beri. Considerations such as these led to the conclusion expressed in 1919 that although vitamin deficiency is an essential aetiological factor in beri-beri, nevertheless it is rarely so complete as to be the sole agent in its causation—a conclusion found to be 'in remarkable agreement with the clinical observations on beri-beri in Mesopotamia' during the late war.

It was thought necessary, therefore, to examine afresh the relation of rice to tropical beri-beri in India. This was the more urgent since it had been suggested to local governments—as the outcome of a resolution passed at the Far Eastern Congress of Tropical Medicine—that legislation be introduced to prevent the over-milling of rice, or the importation of over-milled rice, with the object of causing the disappearance of beri-beri. It was desirable before any such measure was introduced to be sure that its application would be attended with the desired results.

The present research was designed with the object of examining questions relating: (1) to the conditions of growth of rice—soil, manure, irrigation, duration of crop, etc.; (2) to possible differences in nutritive and vitamin values of different varieties of paddy; (3) to the treatment to which paddy is subjected before milling; (4) to the effects of various milling processes; and (5) to the effects of the culinary procedures to which rice was submitted before its consumption; all of which appeared to bear upon the relationship of beri-beri to the too exclusive use of a rice dietary. It was thought that these investigations might throw light on the peculiar limitation of the endemic to certain areas of the Indian Peninsula; a problem on whose solution the completeness of knowledge in regard to beri-beri depends. It was hoped, also, that the results reached might assist legislators in deciding as to the wisdom or unwisdom of the proposed legislation. Unfortunately, financial retrenchment brought the 'Deficiency Diseases Inquiry' to an end before this programme could be completed; the present report deals with such parts of it as have been completed.

[*Here follows an account of the cultivation, harvesting, milling, steeping, parboiling, whitening and storage of rice in various parts of India, and of the relation of these practices and of food habits to the incidence of beri-beri.*]

II. SUMMARY OF EPIDEMIOLOGICAL OBSERVATIONS

(1) Although the habitat of the users of decorticated rice is not limited to certain narrow tracts of country in Bengal and on the north-east coast of Madras, beri-beri, as an endemic, is limited to these parts of the Indian Peninsula. Sporadic cases or even small outbreaks may occur elsewhere, but they are comparatively few in number and are confined to troops, to the inmates of jails, to certain Chinese communi-

ties, to the crews of ships, and to emigrants from, or former residents in, endemic areas. The statement that 'beri-beri appears when decorticated rice is used for any length of time' does not always apply in India.

(2) Beri-beri 'prevailed extensively' a century ago in the Northern Circars when unpolished or home-pounded rice was in general use. It still prevails extensively in this locality, and home-pounded rice still continues to be used in its country districts.

(3) In the Madras Presidency beri-beri prevails for the most part in localities where raw rice (not necessarily always milled and polished) is in general use; in the Bombay Presidency it does not prevail in localities where raw, milled and polished rice is in general use. Outside the Northern Circars the disease is practically unknown in localities where parboiled (milled and polished) or parboiled (home-pounded and unpolished) rice is in general use.

(4) Beri-beri is six to twenty times less common among the users of home-pounded (unpolished) rice in endemic areas than among the users of raw, milled and polished rice in these areas; the proportion varying in different endemic localities.

(5) The users of parboiled rice may suffer from beri-beri in endemic localities, although it is less common among them than among the users of raw, milled and polished rice.

(6) While it is probable that unpolished and parboiled rices may afford protection against beri-beri in localities where it is not endemic, it is certain that they do not always afford protection against it in localities where it is endemic.

(7) In two similar coastal districts in the same latitude where the cultivation of rice is extensive, and where rice is the staple article of diet of large sections of the community, the occurrence or non-occurrence of beri-beri would appear to be related rather to the nutritive and vitamin value of the foods commonly used to supplement the staple diet of rice than to the rice itself. *Atta* (freshly-ground whole wheat flour), milk and milk products are important protective agents. *Ragi* (*eleusine coracana*), so generally used by the poor in Madras, does not prevent beri-beri in endemic areas, even when it forms the staple article of diet.

(8) While in the Madras Presidency there is a rough parallelism between the distribution of modern rice mills, producing raw milled rice, and the distribution and incidence of beri-beri, there is none in the Bombay Presidency where the malady is practically non-existent in the civil population.

(9) The export of rice from the endemic areas of the Madras Presidency is not associated, to any appreciable extent, with the spread of beri-beri whether the rice exported be parboiled or raw. Raw rice pro-

duced in the Bombay Presidency is not associated with beri-beri either in the places from which, or to which, it is exported.

(10) No evidence has been found which would tend to associate the storage of paddy with the prevalence of beri-beri in the Madras Presidency.

(11) A connection between the storage of parboiled rice and the occurrence of beri-beri is said to exist in Rangoon. The limited evidence available did not suggest that the deterioration of rice from storage, or the generation therein of a poison, was an essential factor in the development of beri-beri among the users of home-pounded rice in endemic areas of the disease in the Madras Presidency. Judgement on this matter is, however, reserved.

(12) Hindus, who adhere most strictly to the use of rice as the staple article of diet, suffer less from beri-beri than other classes of the native community in endemic areas of the disease in the Madras Presidency.

(13) Beri-beri only occurs in those jails, in the Madras Presidency, which are located in endemic areas of the disease, although the scale of diet in all jails is the same.

(14) Madrassi troops, especially those recruited from endemic areas of beri-beri in the Madras Presidency, are much more likely to be attacked by this disease in the military stations outside endemic areas than other details of the Indian Army.

(15) The food grains other than rice—millet and maize—cultivated in the Madras Presidency are not of a quality calculated to afford protection against beri-beri in endemic areas, either when used as supplements to a staple diet of rice or as substitutes for rice.

(16) Unknown factors peculiar to, or more potent in, 'endemic areas' of beri-beri appear to possess an important significance in regard to the genesis of this disease.

Finally, it may be mentioned, as a point of interest, that Indian *hakims* of a century ago treated beri-beri in addition to the use of native remedies by advising their patients to substitute 'a milk and wheat' diet for their habitual diet of rice. These foodstuffs supply those elements and complexes in which the rice diet is deficient: suitable protein, mineral elements and vitamins.

[*Here follows an account of the source, variety and description of forty-seven samples of paddy and rice, of which the nutritive and approximate vitamin-B values were determined, and of the chemical composition of the soils on which they were grown.*]

III. SUMMARY OF RESULTS OF EXPERIMENTAL INVESTIGATIONS

(1) The nutritive values of different varieties of paddy vary; and probably also their vitamin values.

(2) The boiling and steaming of paddy ('parboiling') with subsequent drying in the sun, reduces its nutritive value. The reduction is approximately the same for all varieties of paddy; it is related to loss of vitamins A and B consequent on the action of heat and oxidation.

(3) Parboiled paddy does little more than support young birds, fed exclusively upon it, at maintenance. Some varieties do not do that; the milled and polished rices prepared from these may cause *polyneuritis columbarum* if their use be long-continued, especially in young and growing birds.

(4) The rices commonly prepared from paddy in India range themselves, in order of nutritive and vitamin values, as follows: (1) raw, milled, unpolished rice; (2) parboiled, milled, unpolished rice; (3) parboiled, milled rice, slightly polished; (4) parboiled, milled rice, highly polished; and (5) raw, milled and polished rice. The first is the most nutritious and contains most vitamin B; the last is the least nutritious and contains least vitamin B.

(5) Parboiled rices, although highly polished, do not generally cause polyneuritis in pigeons although some may do so if their use be sufficiently long-continued. Parboiling is the surest way of 'fixing' vitamin B in the milled-rice grain.

(6) Some parboiled rices cause ophthalmia in pigeons; this is related to the loss of vitamin A sustained in the process of parboiling.

(7) A parboiled rice, although it may contain a sufficiency of vitamin B to prevent the appearance of polyneuritis in pigeons for 100 days, yet may not suffice to maintain them in vigorous health nor to meet all exigencies; this is especially so in certain individuals.

(8) The nutritive and vitamin values of rices, to all appearances milled and polished in the same way, vary within certain narrow limits.

(9) Both the nutritive value and the vitamin value of rice are reduced in proportion to the degree of polishing to which the rice is subjected. The vitamin value does not always run parellel with the nutritive value.

(10) If the 'unit of vitamin-B value' be taken as 'that amount of vitamin B required daily to keep a pigeon weighing 250 gm. at maintenance without the development of polyneuritis', then the average vitamin-B value of raw, milled and polished rice is a fraction of that unit: namely, 0·4; while the average vitamin-B value of parboiled, milled and polished

rice is approximately double that figure. The vitamin-B values of the raw, milled and polished rices examined ranged between 0·22 and 0·62; those of parboiled, polished rices between 0·75 and 1.

(11) No raw, milled and polished rice in common use in India is wholly devoid of vitamin B. There is always a remnant of this substance in the grain that is removable by washing or destructible by autoclaving.

(12) Washing of rice—whether parboiled or raw—greatly reduces both the nutritive and the vitamin value of the rice. A parboiled rice may be reduced by washing to the status of a raw, milled and polished rice.

(13) No strict parallelism exists between the power of a given rice to cause or prevent *polyneuritis columbarum* and its association with human beri-beri. In India, 'beri-beri-producing rices' are not devoid of vitamin B although they contain an insufficiency of it.

(14) A beri-beri-like malady—characterized by polyneuritis, large heart, hydropericardium, gastro-intestinal derangement, and enlargement of the liver and adrenals—has been produced in pigeons fed exclusively on rice (from Masulipatam) known to have been habitually eaten by sufferers from beri-beri. This rice, which is credited with being 'beri-beri-producing', appears in fact to be beri-beri-producing; twenty-seven other rices examined were not beri-beri-producing although the majority of them caused *polyneuritis columbarum.*

(15) A certain rice from Vizagapatam known to have been habitually eaten by sufferers from beri-beri caused *polyneuritis columbarum* only after the lapse of eighty-nine to ninety-five days. Beri-beri in the human subject may thus be associated with the use of a rice whose status is that of parboiled rice.

(16) Pigeons exhibit wide variations in individual susceptibility to vitamin-B deficiency as evidenced by the development of polyneuritis; the more complete the deficiency the less, as a general rule, is the variation in individual susceptibility; up to a certain point—represented by a vitamin value of the rice of approximately 0·58—the less complete the deficiency the greater, as a general rule, is the variation in individual susceptibility; when this point is passed and as the vitamin value of the rice approaches the unit 1, variation in individual susceptibility again diminishes. Similar variations in the body-weight of individuals are also observed: the greatest variation occurring with rices whose vitamin values are round about 1.

(17) Birds held at maintenance on an exclusive diet of parboiled rice are peculiarly susceptible to sudden reductions in intake and assimilation of vitamin B.

(18) Birds which have once suffered from polyneuritis, and have been cured of it, are more prone to develop the malady than others not previously affected by it. They may even have a recurrence of polyneuritis weeks after 'cure', although they have had access during these weeks to vitamin-rich food.

(19) The clinical and pathological facies of *polyneuritis columbarum* may vary with variations in the composition of the deficient food and with the intervention of other factors such as exposure to cold and damp.

(20) The incidence and variety of the maladies from which pigeons fed exclusively on rice may suffer is governed by the degree of vitamin deficiency of the rice, and by the chance intervention of microbic or other pathogenic agents. The carrier of the specific agent of a given disease may become a subject of this disease when fed on a rice diet deficient in vitamin B.

(21) The forms of 'polyneuritis' from which pigeons fed exclusively on the rices in common use in India may suffer are: (a) the polyneuritis of avitaminosis usually spoken of as *polyneuritis columbarum*; (b) *beri-beri columbarum*, and (c) *infective polyneuritis*. The first is due solely to vitamin-B deficiency; it is characterized by polyneuritis with atrophy of the heart, liver, etc., and hypertrophy of the adrenals. *Beri-beri columbarum* is due to insufficiency but not complete lack of vitamin B acting in association with some unknown agent possessing a specific action on the heart. It is characterized by polyneuritis, large heart, enlargement of the liver and adrenal glands and hydropericardium with or without generalized oedema. *Infective polyneuritis* is due to a bacterial agent whose operation is favoured by vitamin-B deficiency. Similar diversity in aetiology may be expected in regard to the polyneuritic maladies of man that are included under the generic term—beri-beri.

(22) The basal factor in the causation of beri-beri in India is a fundamentally poor diet, whether of rice or other food grains, which provide an insufficient supply of vitamin B, but which is not completely lacking in this vitamin. It is assumed, as a result of the experimental production of beri-beri in pigeons, that some unknown agent, possessing a specific action on the heart, is also concerned in the production of this malady in man.

[*Here follows an account of the chemical investigation of various paddies and rices from localities in which beri-beri is endemic and from others in which the disease is not endemic.*]

IV. SUMMARY OF CHEMICAL INVESTIGATIONS

(1) Boiled paddy is in general poorer in phosphoric acid than raw paddy. The average percentage content of raw paddy in phosphoric acid is 0·65; of boiled paddy, 0·53.

(2) Parboiled, milled and polished rices are in general richer in protein, magnesia, potash and phosphoric acid than raw, milled and polished rices.

(3) The average percentage content of phosphoric acid in parboiled, milled and polished rice is 0·4, that in raw, milled and polished rice 0·3. It depends on the degree of polish: the higher the polish the lower the phosphoric-acid content.

(4) Milling of rice compared with pounding results in a loss of protein, fat, potash, soda, magnesia, alumina, and phosphoric acid.

(5) The average percentage content of phosphoric acid in parboiled, pounded (or unpolished) rice is 0·5, that in raw, pounded (or unpolished) rice is 0·45. Nevertheless, the nutritive value of the latter is higher than that of the former.

(6) A certain parallelism exists between the percentage of phosphoric acid and the vitamin-B content of raw, milled and polished rice; no such parallelism is evident in the case of parboiled, milled and polished rice. Nevertheless, the percentage of phosphoric acid in two rices may be the same and yet one contain less vitamin B than the other.

(7) A parboiled rice may be capable of causing polyneuritis in pigeons although its content of phosphoric acid be over 0·4 per cent.

(8) Raw, pounded or unpolished rices, having an average phosphoric-acid content of 0·45 per cent, are known to be associated with beri-beri in endemic cases.

(9) Certain rices from Masulipatam and Vizagapatam known to have been habitually eaten by sufferers from beri-beri contained 0·45 per cent of phosphoric acid. Masulipatam rice was associated with the occurrence of *beri-beri columbarum* in the laboratory.

(10) Although the percentage of phosphoric acid in a given rice is a fairly reliable indicator of its vitamin-B content, and of its capacity to cause or prevent *polyneuritis columbarum*, it is not a reliable indicator of its capacity to cause or prevent human beri-beri in endemic areas of this disease. A rice which contains over 0·4 per cent of phosphoric acid may be associated with *beri-beri columbarum* in the laboratory or with human beri-beri in endemic areas of this disease, while a rice which contains less than 0·4 per cent of phosphoric acid often forms the staple article of diet in localities where the disease is unknown. It is true that

the lower the content of phosphoric acid in a given rice the more likely is this rice to be associated with beri-beri in endemic areas; but the percentage of phosphoric acid in rice commonly used in endemic areas may be as high as 0·45 to 0·5 and yet beri-beri may occur among the users of it.

(11) Washing of rice causes a great loss of mineral ingredients: iron, alumina, lime, magnesia, potash, soda, soluble silica and phosphoric acid. The percentage of phosphoric acid in raw, milled and polished rice is reduced by the washing of the rice from an average of 0·3 to an average of 0·14. This loss of phosphoric acid is associated with a fall in the vitamin value of the rice. The higher the phosphoric-acid content of rice the greater the loss resulting from washing.

(12) The higher the polish of rice the lower is its percentage content of phosphoric acid.

V. CONCLUSION

The results of this research indicate the extent to which present-day views in regard to the association of endemic or true tropical beri-beri with the too exclusive use of a rice diet require modification in so far as India is concerned.

Beri-beri Columbarum[1]

I. DEFINITION OF BERI-BERI

There are three elements in beri-beri—the multiple neuritis, the cardiac derangement and the oedema—each is important, and as characteristic of the disease, as the other. But there is great variety in their degree and combination in different cases. In some all three elements are equally in evidence and we have the complete clinical picture of true tropical beri-beri, commonly spoken of as 'wet beri-beri'. In others the cardiac element predominates, the neuritis appearing of slight consequence in comparison and sometimes even escaping notice by the inexperienced. In others the oedema is absent or disappears at some stage in the course of the disease, when the condition is spoken of as 'dry beri-beri'. In others again, a greater or lesser degree of peripheral neuritis and muscular wasting may be the only or the chief symptoms of the disease. Some subjects are 'atrophied to skeletons, others are swollen with dropsy, and some show just sufficient dropsy to conceal the atrophy the muscles have undergone' (Manson).

Pathologically, beri-beriis characterized (1) by degenerative changes in the entire nervous system, particularly in the peripheral nerves, the cord, the vagus and the sympathetic system; (2) by diffuse parenchymatous degeneration of the muscles, combined at times with hyaline and fatty degeneration; (3) by hypertrophy and dilatation of the heart, most marked on the right side, with fine fatty degeneration and fragmentation of its muscle fibres; (4) by oedema and serous effusions: anasarca, hydropericardium, hydrothorax and ascites, one or other or all of which may be present in the same case; (5) by chronic passive congestion of the abdominal viscera, especially of the liver, spleen and kidneys; and (6) by congestion of, and ecchymoses into, the mucosa of the stomach and duodenum. To these is often added enlargement, with increased adrenaline content, of the adrenal gland. 'None of these conditions are alone diagnostic of beri-beri. But the combination of nervous lesions, enlarged and dilated right heart, anasarca and effusions, congestion of abdominal organs, and the ecchymoses described, is diagnostic of beri-beri. There is no other disease that presents this peculiar combination of pathological findings.' This state will be referred to throughout the memoir as 'True Beri-beri'.

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[1] Extract from number 4 in List of Books and Memoirs.

II. OBJECTS OF THE RESEARCH

The objects of this research were: (a) to ascertain whether a condition conforming to the above definition could be produced in animals under experimental conditions, by means of diets consisting exclusively of rice or of rice in combination with other articles of food such as are commonly used with it in India and Burma; (b) to determine whether the reputed beri-beri-producing properties of certain rices were due to toxic substances contained in these rices or to deficiency of certain vitamins; and (c) if successful in the production of true beri-beri in animals, to learn the extent to which the dietetic conditions associated with it conformed to those associated with beri-beri in the human subject.

Pigeons were employed for the purpose; large numbers (1,872) being used in order to avoid, as far as possible, the experimental pitfalls into which the use of small numbers is so likely to lead; and in order also to provide sufficient material for statistical study. Rats were used for certain subsidiary purposes, such as the determination of the relative amounts of vitamin B in whole rice and in whole wheat.

III. *POLYNEURITIS COLUMBARUM*

So far as I am aware, true beri-beri has not previously been described in pigeons. A polyneuritic state resembling it in many respects has, as is well known, been produced in fowls and pigeons. This state, known as *polyneuritis gallinarum* or *polyneuritis columbarum*, as the case may be, was first observed by Eijkman, in 1897, when its causal relationship to decorticated rice was demonstrated by him. It occurs in birds fed exclusively on polished rice, and is preventable by the addition to the rice of the polishings removed in the process of milling. As small an amount of the purified vitamin hydrochloride as 2 to 2·5 parts in 1 million parts of washed, polished rice suffices to prevent polyneuritis in pigeons. It is sometimes, though not always, curable by the oral administration of rice polishings or of other vitamin-B-containing material.

Polyneuritis columbarum may be defined as a specific form of starvation resulting from the almost complete absence of vitamin B from the food, and characterized by the loss of appetite, generalized wasting, subnormal temperature, slowed respiration, asthenia, intestinal fluxes, and symptoms referable to functional derangement of the nervous system. Pathologically, it is characterized by degenerative changes in small and variable proportion of the cells of the central and sympathetic nervous systems, diminution in size of the heart, enlargement of the adrenal glands, atrophy of all other organs of the body (the pituitary body in males excepted), muscular wasting, thinning of the bones, degenerative changes in the gastro-intestinal tract, diminution in blood volume, quantitative changes in the cellular elements of the blood, anaemia, acidosis, oedema or serous effusions in a relatively small proportion of cases, and other features which are, in the main, the outcome of starvation. While a number of these features are similar to those present in true beri-beri, the complete clinical and pathological picture of *polyneuritis columbarum* is not, as I pointed out in 1919, the complete clinical and pathological picture of 'true beri-beri'. The latter, in its fully developed form, is something more than the manifestation of a specific form of starvation. Nevertheless, human beri-beri being of so protean a nature, it is possible that one variety of it (in which polyneuritis and general wasting are the chief or only symptoms) may be the counterpart of *polyneuritis columbarum*. If this be so, the condition might properly be spoken of as *polyneuritis hominum* in contradistinction to *beri-beri hominum*. Having said this much, it must be added that the discovery by Eijkman of *polyneuritis gallinarum*, and of its relationship to rice, laid the foundation of our knowledge regarding the aetiology of at least one type of disease included under the generic term 'beri-beri'.

IV. DIAGNOSIS OF *BERI-BERI COLUMBARUM*

It is not possible to distinguish clinically between *polyneuritis columbarum* and *beri-beri columbarum*. In both the polyneuritic symptoms, the head retraction, the 'fits' and other features are to all appearances the same: these have been sufficiently described elsewhere. Nor is there, apart from the polyneuritis, any close clinical resemblance between *beri-beri columbarum* and *beri-beri hominum*. Birds do not exhibit oedema of the feet and legs, while their feathered state does not readily permit of the recognition during life of subcutaneous oedema; nor is the recognition of effusion into the serous sacs nor the nature of the cardiac derangement practicable in these animals during life. In making a diagnosis of beri-beri in polyneuritic birds reliance has, therefore, to be placed on the various pathological appearances found at post-mortem examination, the diagnosis being based on the correspondence between these appearances and those characteristic of the human disease. In addition to the nervous lesions the following are the features on which the diagnosis of *beri-beri columbarum* depends: (1) enlargement and degeneration of the heart; (2) the presence of oedema or of serous effusions or of both; (3) degeneration of the muscles; (4) chronic passive congestion of the abdominal viscera; and (5) congestion and ecchymoses of the upper and intestinal tract. When all these pathological features are present in birds which exhibited definite signs of polyneuritis prior to death, the diagnosis of true beri-beri of the wet variety can be made. When all are present except oedema or serous effusions the diagnosis of true beri-beri of the dry variety is permissible; when the heart is neither appreciably enlarged nor atrophied, but is obviously degenerated, the diagnosis of beri-beri of a type intermediate between the fully developed disease and *polyneuritis columbarum* may be made; when the heart is obviously smaller than normal, although it may be degenerated, the diagnosis of *polyneuritis columbarum* is appropriate.

All cases of polyneuritis occurring during the course of this investigation were subjected to post-mortem examination and placed in one or other of these three categories in accordance with the pathological appearances presented by them. And since the diagnosis of true beri-beri rests so largely on the presence of cardiac enlargement—which may be due either to hypertrophy or to dilatation or to both—a decision in this regard was reached by weighing the organ in all cases or by its measurement *in situ* or by both means; the resultant figures being compared with normal standards. In this way sufficient material relating to the heart was obtained for statistical examination.

V. THE HEART-WEIGHT IN NORMAL PIGEONS

In order to provide adequate data under this heading, 424 control pigeons were used. The birds were arranged in groups according to their live body-weight. The heart was removed by severing the organ close to its attachment with the great vessels, care being taken not to cut through the auricles (an easy mistake to make); all blood or clot was removed and the heart weighed immediately. Standards of the normal range of heart-weight for each range of body-weight were thus obtained.

Twenty-one birds, in which various pathological lesions were found, were excluded.

The next step was to determine the degree of correlation which existed between the body-weight and the heart-weight in healthy, well-fed birds. For if it could be shown that the correlation was high then, the initial body-weights of experimental birds being known, one would be in a position to say, with reasonable exactitude, to what extent the experimental diets had caused the heart to depart from normal either in the direction of atrophy or of hypertrophy. This statistical examination was undertaken by Mr. E. R. Sundararajan at a stage of the investigation when the material available to him consisted of the original and final body-weights and the heart-weights of 552 polyneuritic and of 348 healthy, control birds. He found that a high correlation did exist between the heart-weight and the body-weight in healthy pigeons ($0{\cdot}7434 \pm 0{\cdot}0162$): the heart-weight increases uniformly with the body-weight.

VI. THE HEART-WEIGHT IN DEFICIENTLY-FED PIGEONS

The investigation consisted in feeding groups of pigeons on various rice or other diets deficient in vitamin B. Mr. Sundararajan found, as a result of his statistical studies, that 'the general effect of the deficient diets was to cause cardiac atrophy; a less common effect was cardiac hypertrophy'. Anticipating our subsequent arguments, it may here be said that while in some of the deficiently-fed birds there was but one influence affecting the heart in others there were two conflicting influences: the one tending to cause cardiac atrophy, the other tending to cause cardiac hypertrophy. The first was insufficiency of vitamin B from which all birds suffered; the second was an additional, and unknown, factor superimposed upon the first. This unknown factor is either the specific excitant of 'true beri-beri' or it imparts to the polyneuritis resulting from vitamin insufficiency the pathological characters of 'true beri-beri'. In any large number of birds fed on foods of varying degrees of deficiency of vitamin B there will, therefore, be found all gradations of the polyneuritic state from *polyneuritis columbarum* at the one extreme to true beri-beri at the other, depending on the degree of the deficiency, the presence in the afflicted birds of the unknown excitant of beri-beri, and on the severity of action of the latter.

Taking into consideration the general effect of the deficient diets, Mr. Sundararajan's statistical studies led him to subdivide the 552 deficiently-fed and polyneuritic birds with which he had to deal into three categories as determined by the weight of the heart:

Category A included those birds whose heart-weights exceeded the mean heart-weight of controls; in these some specific factor had caused cardiac hypertrophy.

Category B included those birds whose heart-weights fell between the mean heart-weight of controls and that of deficiently-fed birds; in these some specific factor tended to counteract the general effect of the deficient diets in causing cardiac atrophy.

Category C included those birds whose heart-weights fell below the mean heart-weight in deficiently-fed birds; in these no specific factor was present tending to cause cardiac hypertrophy or, if it were present, it failed to counteract the effect of the deficient diets in causing cardiac atrophy.

As has been stated, the diagnosis of *beri-beri columbarum* was in all cases made by me on pathological grounds alone, and prior to Mr. Sundararajan's statistical examination of the material. His study confirmed my diagnosis in a remarkable way; and his three categories coincided closely with the three arbitrary divisions into which I had divided my material on pathological grounds. His Category A corresponded to my class, true beri-beri; his Category B to my class, intermediate type beri-beri; and his Category C to my class, *polyneuritis columbarum.*

VII. OTHER FACTORS AFFECTING THE HEART-WEIGHT IN DEFICIENTLY-FED PIGEONS

The diagnosis of 'true beri-beri' cannot be made on the weight of the heart alone, although it is one of the most reliable of the means available for arriving at a diagnosis: the pathological appearances of the organ, presently to be described, have to be taken into consideration. Nor is cardiac atrophy always attributable to vitamin deficiency. Some birds in every experiment refuse to eat the defective food or their appetite is so poor that the intake of food falls far below normal requirements. Inanition is thus a complicating factor which must be excluded as far as possible, since in human beings beri-beri does not arise as a result of starvation *per se* nor do diets in use by sufferers from *beri-beri hominum* cause cardiac atrophy. Similarly, intercurrent diseases may affect the weight of the heart either in the direction of atrophy or of hypertrophy. Accordingly, I have excluded all cases in the present series in which intercurrent disease or starvation (whether from refusal to eat or from causes such as ophthalmia) was a prominent feature.

Cases of polyneuritis, in which the weight of the heart fell below the minimum in controls, have likewise been excluded. To this rule there have been a few exceptions; in these the presence of well-marked cardiac dilatation and degeneration has appeared to justify their inclusion. In this way cases of 'other disease', of pure starvation, and of polyneuritis associated with starvation have been weeded out, and we are left only with polyneuritic birds whose heart-weights fell within the normal range of heart-weight in controls (the great majority) or exceeded the maximum in controls and with polyneuritic birds whose hearts, though weighing less than the minimum in controls (a small minority), presented pathological appearances which seemed to justify their inclusion. A fairly just appreciation of the beri-beri-producing potencies of the experimental diets and of their effects upon the heart was thus made possible.

VIII. THE BERI-BERI HEART IN PIGEONS

The macroscopical characters of the 'beri-beri heart' are as follows: It is obviously enlarged, whether the enlargement be due to hypertrophy or to dilatation or to both, and whether or not it be associated with an increase in weight of the organ; a greater or lesser degree of dilatation is almost invariably present, usually confined to the right side; fatty degeneration, sometimes limited to circumscribed areas, sometimes widespread, is an almost constant feature, while fibrotic areas may be present, usually at the apex; some oedema may occur at the auriculo-ventricular junction or extend beneath the serous surface of the organ; engorgement of the superficial vessels is an almost constant feature, it is often extreme and frequently associated with ecchymoses and flame-shaped haemorrhages beneath the serous surface of the organ. Such ecchymoses may be confined to limited areas, commonly on the right side of the heart, or be widespread over its whole surface. Usually, but not invariably, hydropericardium is present.

When to these features is added an increase in weight of the heart over the maximum heart-weight of control birds whose body-weight corresponded to the initial body-weight of the polyneuritic birds, and when the other pathological characters of the malady are present (oedema, serous effusion, congestion of abdominal organs and ecchymoses beneath the mucous surface of the duodenum and upper intestine) the diagnosis of true beri-beri is not in doubt. Nor is it in doubt when the heart-weight falls between the mean and maximum heart-weight of control birds. But the case is different when the heart-weight falls below the mean heart-weight of controls even though the organ be enlarged as a result of dilatation. To meet this difficulty my practice has been to determine the size of the heart by actual measurement before its removal from the body. These measurements were transferred to squared paper and a freehand drawing of the organ made round them. They were then compared with a similar series for controls. In this laborious way a second group of cases was provisionally classed as intermediate type beri-beri. Mr. Sundararajan's statistical classification now seems to make this method unnecessary and polyneuritic birds having degenerated hearts may be grouped in this intermediate category if their heart-weights fall between the mean heart-weight of deficiently-fed birds and that of controls. Sometimes cases are encountered in which the heart, while presenting all the other characters of the beri-beri heart, is of lesser weight than the mean heart-weight in deficiently-fed birds. These I have classed with *polyneuritis columbarum* although it is recognized that if a similar condition existed in man, it would, in all probability, be diagnosed clinically as beri-beri.

IX. FUNDAMENTAL POVERTY OF WHOLE RICE IN VITAMIN B

It is generally assumed that the reason why beri-beri is so common in rice-eating races is because of the milling and polishing processes to which rice is subjected prior to its consumption. This is true enough, but it is only part of the truth. Accordingly, a number of misleading statements are current in the literature of this subject: misleading because they do not represent the whole truth. Such statements are the following:

(1) 'When decorticated rice is used as the main staple of the diet for any length of time beri-beri appears.' This is not necessarily so, and in India it is commonly not so.

(2) 'Outbreaks of the disease disappear when whole or under-milled rice is substituted for decorticated rice.' This may or may not be so.

(3) 'Beri-beri never appears when under-milled or home-pounded rice only is used.' This is not so in India, though it may be so in other countries where a freer use is made of supplementary foods.

(4) 'Beri-beri does not occur when parboiled rice is eaten.' This is not so in India.

(5) 'A rice which contains over 0·4 per cent of phosphorus pentoxide

(P_2O_5) will not cause beri-beri.' This is often so, sometimes it is not so.

(6) 'The incidence of beri-beri depends on the treatment to which rice is subjected before consumption.' There is a great deal of truth in this statement; the treatment to which it is subjected, includiing, however, not only milling and polishing but washing in many changes of water before the rice is used by the consumer.

The chief reason why beri-beri is so common in certain rice-eating races in India is because of the fundamental poverty of the whole rice grain in vitamin B, different kinds of whole rice differing considerably in their content of this factor. The poverty of rice in vitamin B as compared with whole wheat is indicated by the results of the following experiment: Five groups of six young rats of the same age, and of approximately the same initial body-weight and growth potential, were confined each in a separate cage and fed as follows (the food consumption of each animal being carefully measured): one group received a basal diet consisting of 20 parts of 'meat residue', 60 parts starch, 10 parts of fats (olive oil), and 5 parts of 'salt mixture'; no growth resulted while polyneuritis was produced, thus demonstrating the complete, or almost complete, absence of vitamin B from this diet. A second group received the same basal diet plus one gramme of whole rice daily as the sole source of vitamin B, the rice being administered separately; a rate of growth, amounting to 28 per cent, resulted after forty-seven-days' consumption of this diet. A third group received the same diet as the second, plus cod-liver oil to increase the vitamin-A content of the food; the rate of growth was nearly doubled in consequence of this addition and reached 52·2 per cent. A fourth group received the same diet as the second, plus cod-liver oil and yeast to increase both the vitamin-A and vitamin-B content of the food; the rate of growth was quadrupled by the addition of the two vitamins, and reached 113 per cent. The fifth group received the same diet plus one gramme of whole wheat as the sole additional source of vitamins; the rate of growth amounted to 149 per cent in the same period, being five times greater than that resulting from the same amount of whole rice. It is clear, therefore, that even before rice is subjected to any milling processes whatever, it is fundamentally poor in both vitamin A and vitamin B. In comparison with wheat it contains less manganese. At the very best the whole rice grown in endemic areas of beri-beri in the Madras Presidency has no vitamin B to spare for removal by refined milling processes. Human experience has, unwittingly perhaps, devised 'parboiling' as a means of preserving this factor; a procedure, however, which reduces its contents of vitamin A.

X. EFFECT OF PARBOILING, MILLING, POLISHING AND WASHING ON THE VITAMIN VALUE OF RICE

The poverty of rice in vitamins is further enhanced by the various milling processes to which it is subjected before it reaches the consumer. The experimental procedure adopted in determining the effects of these processes was as follows: groups of six pigeons, of the same initial body-weight, were fed exclusively on the different products of the same rice (*Red Samba Paddy*) which was specially grown and milled for me. One group received the raw paddy (unhusked); a second, the parboiled paddy (unhusked); a third, the raw, husked, unpolished rice; a fourth, the parboiled, husked, unpolished rice; a fifth, the milled and lightly polished, parboiled rice; a sixth, the milled and highly polished, parboiled rice; and a seventh, the milled and highly polished, raw rice. The effects of these various products of the same paddy in causing loss of weight (indicating the reduction in nutritive and vitamin value of the rice caused by the various processes to which it was subjected) are shown in a chart. It will be noted that no amount of milling and polishing of the parboiled rice will reduce its vitamin value below a certain level; but the washing to which the dirty, parboiled rice is subjected by the consumer further reduces it. Washing likewise reduces the vitamin value of raw, home-pounded rice, which is of approximately the same value as highly polished, parboiled rice.

XI. EFFECT OF STORAGE AND DETERIORATION ON THE VITAMIN VALUE OF RICE

Taylor has found that the phosphorus-pentoxide content of rice is reduced by the deterioration which commonly occurs when it is stored in a hot and humid atmosphere. This observation has been confirmed in my laboratory: an undeteriorated Burma rice was found to contain 0·355 per cent of P_2O_5; the same rice after deterioration in the hot and humid atmosphere of Rangoon was found to contain only 0·173 per cent of P_2O_5. With this fall in P_2O_5 content there is probably some corresponding drop in the content of vitamin B, though I have as yet no satisfactory evidence on this point. Fujimaki and Matsumora,however, have 'found that the vitamin-B content diminishes with the preservation (storage) of the rice and also according to the different grades of polishing. In a like manner the catalytic action of the enzyme oxidase is diminished (Higuchi)'.

XII. DIGESTIBILITY OF RICE

The inferiority of rice among cereal foods depends not only on its initial deficiency in vitamins, which is further enhanced by milling, polishing, parboiling and washing, but on its poverty in protein and in mineral salts.

The bulk of the rice-eater's diet is also a factor of importance in determining its nutritive value: its bulk introduces a mechanical factor which interferes with the adequate absorption of protein (McCay) and probably of other substances (vitamins, etc.) essential to normal metabolism.

The relatively poor absorption of protein in a bulky diet of rice may be taken as an indication that the absorption of anti-neuritic vitamin will likewise be poor. So that when we hear of diets consisting of as much as 2½ lb. of washed, deteriorated rice and 2 to 3 oz. of *dhal*, being associated with beri-beri, it is very probable that the vitamin B provided by the *dhal* is not being fully utilized. It will presently be shown that true beri-beri occurs in 23·3 per cent of pigeons receiving a diet of washed, polished rice and *dhal* in which the pulse forms as much as 8 per cent of the total food intake. It seems likely, therefore, that so bulky a diet as one consisting of 2½ lb. of rice and 2, 3 or even 4 oz. of *dhal* would be likely to provide optimum conditions for the development of beri-beri in human beings; and that the more white rice eaten the greater the impediment to the absorption of protective amounts of this vitamin. The danger, then, of using a bulky diet of a cereal fundamentally poor in this vitamin is very great.

XIII. COMPARATIVE VITAMIN VALUES OF WHITE FLOUR AND WHITE RICE

White flour and white rice differ in their content of vitamin B or of fractions of this vitamin. Young 40-day-old rats may be kept alive for seventy days or more on an exclusive diet of American white flour without developing polyneuritis except in rare cases; but they do not grow. It follows, therefore, that while white flour is very poor in growth-promoting factors, it is by no means devoid of anti-neuritic vitamin. While the addition of one gramme of American white flour to a basal diet deficient in vitamin B may prevent polyneuritis in young rats during a period of seventy days, the addition of the same amount of highly polished rice to this diet, as a rule, does not, showing that the polished rice is more deficient in the anti-neuritic factor than white flour. Experiments now in progress in my laboratory appear to indicate that there are two fractions in vitamin B (since this was written, papers have appeared by Goldberger, Roscoe, Chick and Roscoe, demonstrating the dual nature of vitamin B); a growth-promoting fraction and an antineuritic fraction. White flour is less deficient in the latter fraction than white rice; which may to some extent explain the compararive rarity of beri-beri in white-flour-eating races. In the course of this work a number of cases of polyneuritis have been met with in rats whose food contained a high proportion of white flour but their incidence was low. Some of these cases resembled beri-beri very closely, having enlarged and degenerated hearts and oedema in addition to the paralysis, but in these an associated infection (usually pneumonia) was present. When no such infection was present they did not present the complete pathological picture of true beri-beri but one of polyneuritis only. Cases of this kind are as yet too few to enable any definite conclusions to be drawn from them, but in view of certain outbreaks of so-called beri-beri amongst white-flour-eating British troops in India, and in certain military stations outside India, the possibility that there may be an infectious or toxic, as well as a dietetic, element in their causation should be borne in mind. As pointed out in my first memoir, beri-beri-like maladies arising in animals under experimental conditions may be due either to infection alone, to infection superimposed on a state of faulty nutrition, or to nutritional factors only. A similar diversity in the aetiology of beri-beri-like diseases may be expected in man.

XIV. EXPERIMENTAL DATA

The experimental diets are grouped in order of their association with true beri-beri; they range from those which cause neither polyneuritis nor beri-beri in pigeons to those associated with a high incidence of fully developed *beri-beri columbarum.*

Of the 1,680 pigeons used in the experiments 424 were controls fed on well-balanced diets; of these 403 were healthy. Of the remaining 1,256 birds 354, or 29 per cent, died of starvation with or without polyneuritis; 97, or 7·7 per cent, died of ‘other causes’ (ophthalmia, pericarditis, gastro-intestinal disease, epithelioma contagiosum, etc.); and 205, or 16·3 per cent, survived. The remaining 600 birds developed polyneuritis; amongst these there were 219 cases of *polyneuritis columbarum*, 244 cases of intermediate type beri-beri, and 137 cases of true beri-beri. The incidence of true beri-beri in 984 birds fed on the various deficient diets was 13·9 per cent. Each of these polyneuritic states is as much a result of the deficient diets as another, and, if the influence of vitamin deficiency in causing beri-beri be admitted, it is permissible to regard them all as varieties of the same disease. But since some of the deficient diets have a greater tendency to be associated with cardiac hypertrophy, and with the complete pathological picture of beri-beri, than others, the beri-beri-producing potencies of the various diets have been gauged by the strength of this tendency, and they are graded according to the incidence of true beri-beri associated with their use. When so graded, there are a number of diets which do not cause beri-beri at all, others which cause it but rarely, and others which cause it fairly often or even frequently.

XV. DIETS WHICH DO NOT CAUSE *BERI-BERI COLUMBARUM*

Of diets which caused neither beri-beri nor polyneuritis in pigeons there were three:

(1) A starvation diet consisting only of water.

(2) A well-balanced diet of mixed grains.

(3) An exclusive diet of a certain parboiled rice containing anaerobic spore-bearing bacillus credited by Acton and Chopra with the production in rice of beri-beri-producing poisons.

From these observations it is learnt that beri-beri cannot arise in adequately-fed pigeons in this locality (Coonoor) nor in pigeons which receive no food but water. There is no beri-beri-producing influence peculiar to the locality itself. It is further shown that when pigeons are fed exclusively on an unwashed, parboiled rice, containing the bacillus credited by the above-mentioned observers with the production in the rice of a beri-beri-producing poison, the birds did not develop beri-beri; while only one bird developed polyneuritis within the period of 120 days during which the experiment lasted. Bacteriological study of the spore-bearing bacillus present in this rice showed it to have 'the identical characters of the organism' described by Acton and Chopra. From this observation it is clear that *beri-beri columbarum* is not due to the toxin said to be produced in rice by this bacillus.

XVI. DIETS WHICH CAUSED *BERI-BERI COLUMBARUM* IN LESS THAN 10 PER CENT OF BIRDS

Of diets which caused true beri-beri in less than 10 per cent of birds there were three:

(1) A diet composed exclusively of washed rice obtained from a stock in actual use by sufferers from beri-beri in Homelin, Burma. This rice was very deteriorated and to be used at all by human beings it must

have been subjected to much washing: incidence of true beri-beri, 3·1 per cent.

(2) An exclusive diet of raw, milled, lightly polished, washed and autoclaved rice: incidence of true beri-beri, 6·2 per cent.

(3) A diet of raw, milled, highly polished and washed rice to which were added cultures in rice of the rice-bacillus (obtained from parboiled rice) credited with the production of beri-beri toxins. The birds received in addition 5 c.c. of these cultures daily, artificially administered: incidence of true beri-beri, 7·7 per cent.

It follows from these observations: (a) that exclusive diets of rice, which are as devoid of vitamin B as any rices commonly used in India, cause true beri-beri in pigeons but rarely; (b) that the bacillus credited with the production in rice of a beri-beri-producing poison does not exercise any beri-beri-producing effect on pigeons nor do its products, when administered in large dosage in rice cultures; (c) that the washing of a milled rice which is associated with beri-beri in human beings may reduce its beri-beri-producing potency, when it forms the exclusive food of pigeons, although the washing lowers its vitamin value.

XVII. DIETS WHICH CAUSE *BERI-BERI COLUMBARUM* IN 10 TO 20 PER CENT OF BIRDS

Of such diets there were four in ascending order of beri-beri-producing potency:

(1) An exclusive diet of the rice actually used by sufferers from beri-beri in Homelin (Burma), administered to the birds in the unwashed state: incidence of true beri-beri, 11·1 per cent.

(2) An exclusive diet of raw, milled and lightly polished rice which had been subjected to washing by hand-rubbing in fifteen changes of water: incidence of true beri-beri, 11·8 per cent.

(3) A diet consisting for the first 123 days of the experiment of unwashed, parboiled rice containing the bacillus credited with the production of beri-beri toxins, and thereafter, a diet of mixed grains (control diet) autoclaved in an alkaline medium at a temperature of 130° C. for an hour and a half; the experiment being carried out during the hot and relatively dry months of the year: incidence of true beri-beri, 11·8 per cent.

(4) An exclusive diet of raw, milled and lightly polished rice (same as in (2) above) which was autoclaved (not in an alkaline medium) at 120° C. for one hour: incidence of true beri-beri, 13·9 per cent.

As has been shown, the washing of rice markedly reduces its nutritive and vitamin-B values. In this and succeeding groups there are three rices which, when they formed the exclusive food of pigeons, were affected in different ways by washing, so far as their beri-beri-producing potency was concerned. The washing of the Homelin rice reduced its beri-beri-producing potency; while the washing of parboiled rice increased (*vide infra*) its beri-beri-producing potency. A third rice was likewise reduced in beri-beri-producing potency by washing. The explanation of these apparently conflicting results will appear later.

From the observations included under this heading it is learnt: (a) that washing may decrease the beri-beri-producing potency of one rice and increase the beri-beri-producing potency of another, when it forms the exclusive food of pigeons, although washing reduces the nutritive and vitamin-B values of the rice: (b) that the autoclaving of a certain rice may decrease its beri-beri-producing potency, when it forms the exclusive food of pigeons, although autoclaving lowers its vitamin-B value; and (c) that a diet of mixed grains which maintains pigeons in perfect health can be rendered beri-beri-producing by autoclaving in an alkaline medium, whereby its vitamin value is reduced.

XVIII. DIETS WHICH CAUSE *BERI-BERI COLUMBARUM* IN 20 TO 30 PER CENT OF BIRDS

Of such diets there are six in ascending order of beri-beri-producing potency:

(1) An exclusive diet of raw, milled and lightly polished rice for the first forty days of the experiment, and thereafter, the same rice autoclaved (not in an alkaline medium) for one hour at 120° C.: incidence of true beri-beri, 20 per cent.

(2) An exclusive diet of raw, milled and lightly polished rice having fragments of pericarp adherent to some of the grains and administered to the birds in the unwashed state: incidence of true beri-beri, 21 per cent.

(3) A diet composed of raw, milled, highly polished and washed rice plus 0·8 gm. (in this experiment each bird was given 0·4 gm. of *dhal* daily for the first four days; thereafter 0·8 gm.) of *dhal arhar* per bird daily, the latter administered artificially: incidence of true beri-beri, 23·3 per cent.

(4) An exclusive diet of greatly deteriorated rice, similar to that used by sufferers from beri-beri in Rangoon: average incidence of true beri-beri, in two experiments, 24·9 per cent.

(5) An exclusive diet of parboiled rice from Coimbatore which contained in its interior a bacillus credited with the production of beri-beri-producing toxins; the rice being administered to the birds after washing

by hand rubbing in fifteen changes of water and drying in the sun: incidence of true beri-beri, 27·3 per cent.

(6) An exclusive diet of parboiled and greatly deteriorated rice used by sufferers from beri-beri in Vizagapatam and Masulipatam; administered to the birds in the unwashed state: incidence of true beri-beri, 29·4 per cent.

From these observations it is learnt: (a) that the addition of 0·8 gm. of *dhal arhar*—forming approximately 8 per cent of the food of the birds—to an exclusive rice diet capable of causing not more than 6·2 per cent of true beri-beri in pigeons, increased its beri-beri-producing potency to 23·3 per cent; (b) that an exclusive diet of lightly milled and polished rice, having fragments of pericarp adherent to some grains and similar to the home-pounded rice which sometimes forms the exclusive food of residents in parts of the Madras Presidency, may cause true beri-beri in 21·0 per cent of pigeons fed exclusively upon it; (c) that this lightly milled rice when washed or autoclaved may have its beri-beri-producing potency reduced although these processes reduce its nutritive and vitamin-B values; (d) that certain deteriorated rices, associated with beri-beri in human beings, when given to pigeons as their exclusive food, may cause true beri-beri in 24 to 29 per cent of the birds. Finally, it is shown that a parboiled rice, containing a bacillus credited with the production of beri-beri poisons, which in its unwashed and presumably most 'toxic' state is incapable of causing beri-beri in pigeons, gave rise to the fully developed disease in 27·3 per cent of pigeons after it has been washed and dried in the sun, thus demonstrating that this rice contained no beri-beri-producing poison, but that beri-beri-producing properties were imparted to it by the reduction brought about in its nutritive and vitamin values by washing.

XIX. DIETS WHICH CAUSE *BERI-BERI COLUMBARUM* IN 30 TO 40 PER CENT OF BIRDS

Of such diets there are three in ascending order of beri-beri-producing potency:

(1) A diet of mixed grains autoclaved in an alkaline medium at a temperature of 130° C. for one and a half hours; the experiment being carried out in winter during the rainy season: incidence of true beri-beri, 36·6 per cent.

(2) A diet composed of washed, parboiled rice and whole *ragi* (millet) for the first thirty-two days of the experiment; and thereafter of washed, autoclaved, raw, polished rice and *ragi*, the *ragi* being administered artificially and comprising for the greater part of the experiment as

much as 20 to 25 per cent of the total food intake: incidence of beri-beri, 40·5 per cent.

(3) A diet composed of raw, milled, highly polished and washed rice *plus* 2 gm. of whole *ragi*, the latter being administered artificially, and comprising on the average about 20 per cent of the total food intake. During the latter stages of this experiment the birds consumed only 5 to 8 gm. of the polished rice; their food at this period contained, therefore, approximately 25 per cent of whole millet: incidence of true beri-beri, 41·0 per cent.

From these observations it is learnt: (a) that a diet of mixed grains which maintains pigeons in perfect health will cause true beri-beri in 36·6 per cent of pigeons (fed upon it during the north-east monsoon in this locality) when it is autoclaved in an alkaline medium thereby having its content of vitamin B reduced; (b) that the addition of 20 to 25 per cent of whole *ragi* (millet) to rices which cause true beri-beri but rarely, when they form the exclusive food of pigeons, renders the food highly beri-beri-producing; true beri-beri arising in 40 per cent of pigeons fed upon the rice and *ragi* mixture.

XX. DIETS WHICH PREVENT *BERI-BERI COLUMBARUM*

Among the experimental diets there were three greatly deteriorated rices obtained from stocks in actual use by human sufferers from beri-beri or which were similar to those in use by beri-beri subjects. When pigeons were fed exclusively on these rices in the unwashed state true beri-beri was produced in 24·9, 11·1, and 29·4 per cent of the birds respectively. Only small quantities of the rice described in XVIII, (6) were procurable so that preventive experiments could not be undertaken with it. But of the other two a sufficiency was obtained to enable preventive experiments to be conducted concurrently with those designed to test the beri-beri-producing potency of these rices. In the first experiment one group of twenty birds was fed on deteriorated Burma rice to which certain additions were made at the same time that two other groups (each containing forty-eight birds) were being fed exclusively on this rice. In the two latter groups the average incidence of true beri-beri was 24·9 per cent. In the first group the birds received, with this deteriorated rice, 1 gm. of *dhal* and approximately 1 gm. of *atta* per bird daily. The effect of these additions was to increase the appetite of the birds, so that approximately twice as much of the deteriorated rice was ingested daily as by birds not receiving these additions. The preventive experiment was continued for a period of 150 days, with the result that the birds were completely protected both from polyneuritis and from beri-beri despite their consumption of approximately twice as much of the deteriorated and 'toxic' (?) rice as was eaten by birds not receiving the *dhal* and *atta* in addition to this rice. It follows, therefore, that either there was no beri-beri-producing toxin in this rice or that it was harmless in the presence of adequate amounts of *dhal* and *atta*.

In the second experiment a similar procedure was followed: forty-eight birds received for a period of 126 days a basal diet of deteriorated, Homelin rice, capable of causing 11·1 per cent of true beri-beri in pigeons, together with 2 gm. of *dhal* per bird daily. This amount of *dhal* did not prevent the birds losing weight; consequently, tomato juice was added on the forty-ninth day of the experiment. These additions afforded the birds complete protection against both polyneuritis and beri-beri, although the rice was part of a stock in use by human sufferers from beri-beri, and although the pigeons consumed large amounts of it (20 to 25 gm. daily). It follows, therefore, that supposedly beri-beri-producing rices are harmless, in so far as their capacity to cause beri-beri in pigeons is concerned, when they are combined with adequate amounts of vitamin-rich grains and tomato juice.

XXI. IS *BERI-BERI COLUMBARUM* CAUSED BY A TOXIN OR TOXINS IN THE EXPERIMENTAL DIETS?

The current views regarding the causation of beri-beri are:

(1) That it is due to a toxin or toxins in rice, the action of which may possibly be aided by vitamin deficiency.

(2) That it is due solely to deficiency of anti-neuritic vitamin.

The foregoing experiments have revealed a number of enlightening facts regarding the genesis of this disease in pigeons. In the first place, they demonstrate conclusively that a morbid state having all the pathological characters of human beri-beri can be produced in these birds by means of diets deficient in, but not devoid of, the anti-neuritic fraction of vitamin B; and in the second, that this state is not due to toxins in the rice. Toxins which are stated to be produced in rice by bacterial action are excluded as a cause of *beri-beri columbarum* by the following facts:

(1) A certain parboiled rice contained the bacillus credited by Acton and Chopra with the production in the rice of beri-beri-producing toxins, yet this rice did not cause beri-beri nor oedema when it formed the exclusive food of pigeons.

(2) The same rice after it has been washed, and its vitamin-B content thereby reduced, caused true beri-beri in 27·3 per cent of birds fed upon it. This effect was produced although the washing must have removed

in great part any water-soluble toxin which may have been present in the rice.

(3) When adequate amounts of *dhal*, *atta*, Marmite, yeast and tomato juice were added to the deteriorated rices, used by human sufferers from beri-beri and capable of causing 11 to 24 per cent of true beri-beri in pigeons, the disease was completely prevented although larger amounts of the rices were consumed than by birds fed on the same beri-beri-producing rices without these additions. Either there was no beri-beri-producing toxin in these rices or, if there were, it was wholly deprived of harmful action in the presence of a sufficiency of vitamin B.

(4) A well-balanced diet of mixed grains, which maintained pigeons in perfect health, was rendered highly beri-beri-producing by autoclaving in an alkaline medium. Unless poisonous bases were produced as a result of the autoclaving, the malady was not due to any toxin present in the grains.

I have found no evidence in these experiments to indicate that beri-beri results from a poison produced in deteriorated rice by bacterial action; on the contrary, conclusive evidence has been obtained indicating that such deteriorated rice is harmless, so far as the production of *beri-beri columbarum* is concerned, when adequate amounts of vitamin-rich food are added to it.

XXII. RELATION OF VITAMIN INSUFFICIENCY TO *BERI-BERI COLUMBARUM*

It has been shown that true beri-beri, to the extent of 24 to 29 per cent, may be associated with the use of exclusive diets of certain rices; that is to say, with diets deficient not only in vitamin B but in protein and in inorganic salts, and excessively rich in carbohydrates. True beri-beri may likewise be associated with the use of a well-balanced diet which is for pigeons neither deficient in protein nor in inorganic salts nor excessively rich in carbohydrates, provided this diet be of a certain degree of vitamin insufficiency. The food fault common to both these diets is insufficiency of vitamin B or of the anti-neuritic fraction of this vitamin. This insufficiency is, therefore, the essential food fault concerned in the production of true beri-beri in pigeons.

There are two extremes as regards the vitamin-B value of the diets used in these experiments, neither being for practical purposes associated with beri-beri production. At the one extreme, the food is rich in anti-neuritic vitamin; at the other, it is almost wholly devoid of it. Starting from these extremes true beri-beri can be produced in a relatively high proportion of birds in two ways: (a) either by reducing to a certain level the amount of vitamin B in a diet containing a sufficiency of it, as by autoclaving or washing; or (b) by raising to a certain level the amount of vitamin B in a diet which is almost wholly devoid of it, as by the addition to it of appropriate amounts of *dhal* or *ragi*. The disease can likewise be produced in a relatively high proportion of birds by rice diets which are just at the right level of vitamin insufficiency, as by rices of a certain degree of milling and polishing.

In the first memoir on 'The Relation of Rice to Beri-beri in India', a method was described whereby an approximate numerical value could be given to the vitamin-B content of any rice. The 'unit of vitamin-B value'—designated by the figure 1·0—was defined as the minimal amount of vitamin B required to keep pigeons weighing 250 gm. at a maintenance level for a period of 100 days without the development of polyneuritis. The degree of vitamin deficiency of a given rice diet is found by dividing the average number of days in which the diet causes polyneuritis by 100, allowance being made for differences in the initial, average body-weight of the birds used in different experiments.

The approximate vitamin-B value of the various experimental diets has been arrived at in this way. The nutritive values of the different experimental diets are shown in a similar way: this value being indicated by the average daily loss of body-weight caused by them.

Beginning with an exclusive diet of raw, milled, polished and washed rice, we have a food the vitamin-B value of which is as low as that of any rice diet in use by man; this value is represented by the figure 0·20, which is 80 per cent below the minimal amount of vitamin B required to prevent polyneuritis. When this rice forms the exclusive food of pigeons true beri-beri is produced but rarely: occurring in only 3 per cent of the birds. If now 0·8 gm. of whole *dhal arhar* (per bird daily) be added to the rice diet—forming approximately 8 per cent of the total food ingested—the vitamin value of the food mixture is raised from 0·20 to 0·50, or to a level which is 50 per cent below the minimal amount of vitamin B required to prevent polyneuritis. Associated with this increase in the vitamin-B value of the food the incidence of true beri-beri rises from 3 to 23 per cent. Similarly, if approximately 20 per cent of whole *ragi* be added to the basal diet of highly polished, washed rice, the vitamin-B value of the food mixture is raised from 0·20 to 0·64, or to a level which is 36 per cent below the minimal amount of vitamin B required to prevent polyneuritis. Associated with this increase in the vitamin value of the food the incidence of true beri-beri rises from 3 to 40 per cent.

Going to the other extreme, we find that a diet of mixed grains, which is rich in vitamin B and promotes good growth in young pigeons, becomes beri-beri-producing when its vitamin-B value is reduced by autoclaving from well over 1·0 to 0·8. Associated with this decrease in vitamin value of the food the incidence of true beri-beri rises from 0 to 36 per cent. Similarly, with parboiled rice which in its unwashed state contains 'just enough' (1·0) vitamin B to keep young pigeons at maintenance level and free from polyneuritis: when this rice is washed by hand rubbing in fifteen changes of water its vitamin value is reached from 1·0 to 0·70. This reduction is associated with an incidence of true beri-beri amounting to 27·3 per cent. Again, certain rices, whether parboiled or raw, washed or unwashed, have vitamin-B values of round about 0·6; these also, when they form the exclusive food of pigeons, are associated with an incidence of true beri-beri amounting to from 21 to 29 per cent.

It is thus proven that true beri-beri as it occurs in pigeons is not usually associated with diets which are devoid, or almost devoid, of vitamin B but, on the contrary, with diets which contain appreciable amounts of this vitamin; always provided that they do not contain enough to keep the birds at maintenance level. It is also proven that there is an optimum degree of insufficiency of vitamin B at which *beri-beri columbarum* arises; this optimum is provided by diets having vitamin-B values lying between 0·5 and 0·8. That is to say: a reduction of from 20 to 50 per cent in the minimal amount of vitamin B required to keep young pigeons at maintenance level and free from polyneuritis suffices for the production of true beri-beri. This constitutes the 'danger-zone' of vitamin insufficiency.

The effect of washing in decreasing or in increasing the beri-beri-producing potency of rice will now be understood. If the initial vitamin-B value of a given rice be 1·0, or just below 1·0, as is often the case with parboiled rices, then washing will bring it within the danger zone of vitamin insufficiency (0·5 to 0·8) when it forms the only food of pigeons. If its initial vitamin-B value be 0·5, as is often the case with deteriorated parboiled rices or with raw, milled rices, then washing will lower this value until it falls below the level at which *beri-beri columbarum* is most likely to arise. But such a washed rice is potentially very dangerous: for unless a sufficiency of *dhal* or of other vitamin-rich foods be added to it, the diet may again be brought within the danger zone by the too-sparing use of these supplementary articles of food. This appears to be the reason why deteriorated rice—so commonly used by the poverty-stricken Indian and Burman—is so often associated with beri-beri. Such rice to be used at all must be subjected to repeated washing and the small amount of vitamin-containing foods available to its users may merely serve to bring the food mixture within the danger limits especially if the bulk of rice consumed be large. It seems also to be the reason why beri-beri does occur amongst the users of parboiled and home-pounded rices; the poverty of these people may be such that the addition of any other vitamin-rich food (*dhal*, *atta*, vegetables) to the basal diet of rice is impossible. Judging by the results observed in pigeons, beri-beri must result in a proportion of persons so fed, since the vitamin value of the parboiled or home-pounded rice may, after the preliminary washing to which it is subjected, be optimal for beri-beri production.

XXIII. THE SPECIFIC EXCITANT OF *BERI-BERI COLUMBARUM*

So far it has been demonstrated that a specific food fault—insufficiency of the anti-neuritic fraction of vitamin B—is essential to the production of true beri-beri in pigeons. But it has not been shown that vitamin insufficiency is the ultimate cause of the disease. A general effect of the experimental diets was to cause polyneuritis with cardiac atrophy; this, then, may be said to be a general effect of an insufficiency of vitamin B in the food. But another, though less common, effect was the production of polyneuritis with cardiac hypertrophy (beri-beri). There were, therefore, two contending influences at work in a proportion of the birds: one (vitamin insufficiency) tending to produce polyneuritis with cardiac atrophy; and another (unknown agent) tending to produce cardiac hypertrophy in association with the complete pathological picture of true beri-beri. Statistical studies have demonstrated what was suspected on pathological grounds, viz. the existence of a positive agent, other than the negative agent of vitamin insufficiency, which is the specific excitant of true beri-beri or which contributes to the production of the complete pathological picture of this disease. This specific and toxic agent appears to be produced in greater quantity in some birds than in others and by some diets than by others as, for example, in pigeons fed on a mixture of white rice and whole Indian millet which causes true beri-beri in 40 per cent of them. Since this specific excitant of beri-beri is not a toxin produced in rice nor, as it would seem, in the body by bacterial action, the probability is that it is a poison generated in the body as a result of the disordered metabolism induced by a certain degree of vitamin insufficiency. (Bacteriological studies by Colonel Gloster have failed to reveal any organism which might be credited with the production of *beri-beri columbarum*.) If this be so, the diversity of symptoms and pathological changes which may result from vitamin insufficiency will be determined by the varying biochemical responses of different individuals to this influence, and by the extent to which the specific excitant of true beri-beri is produced within their bodies: in no two individuals may the symptomatic manifestations be precisely alike. It may be expected that the same diversity of symptoms and of pathological change met with in pigeons will be met with also in man, allowance being made for probable variations in vitamin requirements in the two species. Many years ago Eijkman propounded the view that some substance in the cortical layers of rice was necessary to neutralize the otherwise deleterious effect of a diet over-rich in starch. He, as well as Caspari, Moszkowski and others, was of opinion that 'the ultimate cause of beri-beri may yet prove to be a nerve poison produced by a disordered metabolism arising out of vitamin deprivation' (quoted from Walsh). The observations here recorded do not prove, but neither do they disprove, that a nerve poison is produced in the body as a result of insufficiency of vitamin B, nor that vitamin B is required to neutralize the deleterious effect of a diet over-rich in starch; but they do prove that a heart poison is produced in the body as a result of vitamin insufficiency and they suggest that a sufficiency of vitamin B is required to neutralize the otherwise deleterious effect of some component of the diet. It might be argued in connection with the experimental diets of polished rice to which *dhal* or *ragi* were added—thus greatly increasing their beri-beri-producing potency—that it is these additions to the rice, or some component of them (not necessarily their starch but possibly their protein), which provide the beri-beri-producing substance in greater quantity than can be provided by polished rice alone; whether or not this is so I cannot say. But the conception of positively harmful substances generated in the body as a result of a negative food fault is one which research on other diseases has brought into prominence within the last year or so. I am led, therefore, to conclude that the ultimate cause of true beri-beri is a poison produced in the course of a disordered metabolism arising out of insufficiency of the anti-neuritic fraction of vitamin B, and that the view propounded by Eijkman many years ago, and so ably defended by Walsh, is in essence the correct view, though starch is not necessarily the source of this poison.

XXIV. OEDEMA IN *BERI-BERI COLUMBARUM*

Generalized oedema or serous effusions or both were present in 98 out of the 137 cases of true beri-beri in this series, or in 71·5 per cent. There were thus 98 cases to which the term 'wet beri-beri', and 39 cases to which the term 'dry beri-beri' might reasonably be applied. Effusion into the pericardial sac was most common, as also it is most common in man. It occurred with or without—most frequently without—other evidences of oedema in 69·3 per cent of cases of *beri-beri columbarum*. It ranged in amounts from a few drops of clear, amber-coloured fluid to 10 and in rare cases to 15 c.c. Ascites and hydrothorax were equally rare; each was present in 0·73 per cent of cases always in association with generalized oedema. Subcutaneous oedema was fairly frequent; it occurred in approximately 11·0 per cent of cases. It may be comparatively slight or very marked, filling up the groin spaces and extending over the abdomen and thorax and down the thighs. It stops short at the horny covering of the legs.

Oedema or serous effusion or both are more likely to be associated with cases of polyneuritis presenting cardiac hypertrophy and degeneration (true beri-beri) than with cases of polyneuritis without cardiac hypertrophy or with cases of the 'intermediate type'. Thus if the 600 polyneuritic birds be divided into two groups: the first made up of 137 cases of true beri-beri and the second of the remaining 463, the incidence of hydropericardium, ascites, hydrothorax and subcutaneous oedema in the two groups is as follows:

Percentage Incidence of	*True Beri-beri:* 137	*'Polyneuritis columbarum' and Intermediate Type Beri-beri:* 463
Hydropericardium	69·3	36·9
Ascites	0·73	0·64
Hydrothorax	0·73	0·21
Subcutaneous oedema	10·94	5·61

It does not follow, however, that the diets associated with the highest incidence of true beri-beri are always associated with the highest incidence of oedema. There is no evidence which would suggest that the specific agent which causes the cardiac hypertrophy is also the cause of oedema. Nor is any strict parallelism between cardiac hypertrophy and oedema to be expected, for a number of factors are concerned in the oedema production; of these, age, exposure to cold and damp, and the composition of the food are the chief. Oedema is more likely to occur in young than in old birds, during periods of heavy rainfall than at other seasons, and in birds whose food is deficient in vitamin A as well as in vitamin B. Poverty of protein does not appear to have been a factor of much importance in the production of the oedema, since a diet of autoclaved grains, which is richer in protein than an exclusive diet of rice, was associated with a higher incidence of oedema (65·8 per cent) than certain diets composed exclusively of rice.

XXV. EFFECTS OF CERTAIN SUBSIDIARY INFLUENCES ON THE DEVELOPMENT OF *BERI-BERI COLUMBARUM*

1. *Time under Experiment*

Since birds, fed exclusively on highly polished rice, die in an average period of twenty-three days without exhibiting the pathological features of true beri-beri except in rare cases, it might be thought that the reason why they so rarely develop the disease is because this diet does not allow them to live long enough for its development. This is, however, not so. Mr. Sundararajan finds that the number of days under experiment has no bearing on the relationship of the final heart-weight to the initial body-weight of polyneuritic birds; the development of true beri-beri does not, therefore, depend on the length of time during which the birds have been living on the deficient diets. The genesis of the specific factor causing cardiac hypertrophy and degeneration appears to be a matter of individual peculiarity.

True beri-beri has been found in birds dying as early as the twenty-first and as late as the 120th day of experiment.

2. *Loss of Body-weight*

Mr. Sundararajan finds that the total loss of body-weight has no bearing on the relationship of final heart-weight to initial body-weight in birds fed on the various deficient diets. Sometimes the loss of weight is precipitate, sometimes it is more gradual, and not infrequently marked loss of weight occurs only with the onset of symptoms of beri-beri or shortly before their onset.

3. *Composition of the Food*

It is difficult to say to what extent the composition of diets, having approximately the same degree of vitamin insufficiency, may influence their beri-beri-producing potency. Thus two of the diets caused true beri-beri in 11·8 per cent of birds fed upon them; yet the one was an exclusive diet of rice, ill-balanced, poor in protein and in inorganic salts, and excessively rich in starch, and the other a well-balanced diet of autoclaved mixed grains. On the other hand, the addition of *dhal* (*Phaseolus mungo*) or *ragi* (*Eleusine coracana*) to a diet of polished rice definitely increased its beri-beri-producing potency, from which it might be inferred that this increase was due to substances provided by the *dhal* or *ragi*. All that can be said at present is that some of the experimental diets were more likely to cause *beri-beri columbarum* than others; for practical purposes relating to the human disease in India these were diets of polished rice to which other grains (*dhal* and *ragi*) were added in insufficient quantities.

Sudden reduction in the vitamin content of food may precipitate the onset of beri-beri; so also may sudden reduction in the assimilation of food such as may result from antecedent diarrhoea causing the rapid passage of food through the alimentary tract. Acute diarrhoea has often been observed to precede the onset of *beri-beri columbarum*.

4. *Place of Origin of the Birds*

At one stage of this investigation it was thought that birds obtained from endemic centres of beri-beri were more prone to develop the disease than others obtained from non-endemic localities; the first cases of true *beri-beri columbarum* having been observed (1923) in birds obtained from a place where beri-beri occurred. Steps were accordingly taken to elucidate this point: an important one since the possibility of certain birds being 'carriers' of a pathogenic beri-beri-producing agent had to be considered. Birds were obtained in large numbers from the Northern Circars—the endemic home of the disease—and fed, under conditions of the strictest control, on various deficient diets. The incidence of true beri-beri in these birds was not significantly higher than in others, fed on the same diets at the same time, obtained from non-endemic localities; an impression which I had derived from less-extended observations was thus corrected. Nor was it found that deficiently-fed birds suffered from true beri-beri more frequently in one cage than in another; there was in fact no evidence whatever that the disease was due to a microbic or other pathogenic agent capable of transference from the sick to the healthy. Having regard to the work of Hamilton Wright, attempts were made by Colonel Gloster to isolate from the upper intestine bacteria which might prove to have a causal relationship to the disease but with negative results. I have not, therefore, discussed this possibility further, the evidence seeming to point more certainly to a metabolic than to a microbic excitant of the malady.

5. *Sex*

Of the 137 cases of true beri-beri 75 occurred in females and 62 in males; the percentage incidence being 14·3 in females and 13·5 in males. There is, therefore, no noteworthy difference in the incidence of true beri-beri in the two sexes in pigeons confined in cages and subjected to the same conditions of life. A difference of sex incidence is said to occur in human beri-beri; males being more commonly affected than females. This difference would not appear to be due to any peculiar disposition of the male sex to the disease but rather to the more frequent operation in this sex of such factors as overwork and exposure to cold and damp. These, by imposing additional burdens on the metabolic resources of the body, may bear more heavily on some individuals than on others and cause significant differences in the sex incidence of the malady.

6. *Individual Idiosyncrasy*

Of all subsidiary factors concerned in the production of *beri-beri columbarum* individual idiosyncrasy is the chief. On a given diet, birds of like age, sex, plumage and of the same place of origin, may survive for a short or for long periods, show no noteworthy differences in loss of body-weight, and yet at the end of the experiment one may have true beri-beri and another polyneuritis only; while in rare cases birds may survive for periods as prolonged as 120 days without developing either. The investigation has provided no explanation of this varying response of different birds to the same food fault. The instinct of self-preservation is developed to an extraordinary degree in some birds which exhibit remarkable power to select from a number of grains of rice only those having fragments of pericarp adherent to them. There can be little doubt that individual differences in this respect play their part in determining the fate of different birds fed on the same deficient food.

Finally, it may be inferred, from the results of this investigation, that an amount of vitamin B which may 'just suffice' to prevent the development of beri-beri under certain conditions of life may not suffice to prevent it in other circumstances. In connection with human beri-beri it sometimes happens that the inmates of certain institutions or residents in certain places are stated to consume precisely the same food, yet this food is associated with beri-beri in one institution and not in another. Assuming that the food is identical in the two places, then, some factor (such as residence on damp soil, exposure to cold and damp, and debilitating infections) may, other things being equal, suffice to determine the occurrence of the malady, or its higher incidence in one place than in another. In such circumstances the necessary preventive procedure is to increase the vitamin-B components of the food proportionately to the less-favourable conditions of life. An example of this kind, relating to the jails of Burma, will presently be given.

7. *Aetiology of Beri-beri Columbarum*

We are now in a position to define with some certainty the causation of *beri-beri columbarum*: the disease is caused by subsistence on diets containing an insufficiency, but not wholly devoid, of the anti-neuritic fraction of vitamin B. There is an optimum degree of vitamin insufficiency at which beri-beri is likely to arise. This optimum is provided by diets containing from 20 to 50 per cent less vitamin B than the minimal amount required to keep pigeons at maintenance level and free from polyneuritis; diets having greater degrees of vitamin insufficiency are less likely to cause the disease. Under optimum conditions of vitamin insufficiency a poison is generated in the body which exercises a specific effect on the heart, and possibly also on the nervous system and other tissues of the body. This poison is either the cause of the complete syndrome of beri-beri or it contributes to the production of that syndrome. The ultimate cause of the complete pathological picture of beri-beri is not, therefore, a negative but a positive agency though the latter arises as a result of the former. The specific beri-beri-producing agent is produced in greater quantity in some individuals than in others or its effects are more marked in some individuals than in others. Accordingly, there is great variety in the symptomatic and pathological features of the malady. Certain diets appear to give rise to a greater production of this agent than others; those that are most potent in this regard being diets composed of polished rice to which insufficient amounts of *dhal* or of *ragi* are added. The disease, as seen in pigeons, is not due to a toxin in rice; deteriorated rices associated with beri-beri in the human subject are rendered harmless to pigeons by the addition of adequate amounts of *dhal*, *atta*, Marmite, yeast and tomato juice.

Beri-beri is precipitated in its onset and its incidence is increased by cold and damp: it is most likely to be of the wet variety in these circumstances. The 'incubation period' of *beri-beri columbarum* ranges from 20 to 110 days.

XXVI. DIETS ASSOCIATED WITH HUMAN BERI-BERI

As was pointed out in my first memoir, the endemic home of beri-beri in the Madras Presidency is the flat, inundated area which includes the deltas of the Kistna and Godaveri rivers. This locality is devoted to the cultivation of rice to the almost complete exclusion of other more nutritious foods which must be eaten with the rice if nutritional needs are to be satisfied. The dwelling huts of the people are dark, damp, ill-ventilated hovels often raised no more than a few inches above the level of the irrigated fields. Whole families and often whole villages suffer from minor degrees of beri-beri; cases of the fully-developed disease occur for the most part during or after heavy rain.

An inquiry into the dietetic habits of sufferers from beri-beri in this locality was undertaken by one of my assistants, B. G. Krishnan, in order that a comparison might be instituted between the composition of diets associated with *beri-beri hominum* and that of the experimental diets causing *beri-beri columbarum*. The inquiry brought to light a number of interesting facts:

(1) Beri-beri is, in its endemic haunts, essentially a poor man's disease. The well-to-do rarely or never suffer from it; although people of the better-fed classes in certain parts of Ganjam may suffer from 'Epidemic Dropsy'.

(2) The diet of the poorer classes is more often composed exclusively of rice than is generally supposed: of raw, milled and polished rice or of parboiled rice in the towns, and of home-pounded rice in country districts.

(3) Rice-eaters, irrespective of whether the rice be parboiled or raw, milled or unmilled, polished or unpolished, are liable to attacks of beri-beri, though the users of polished rice are in general more liable to the disease than others.

(4) *Dhal* and vegetables form a very small part of the diet of sufferers from beri-beri in this locality.

(5) The disease, in its acute form, is most prevalent during the winter months, coincident with or following the heavy rains of the north-east monsoon.

(6) It commonly makes its appearance following attacks of some debilitating illness (diarrhoea, dysentery) or in sufferers from some chronic debilitating malady.

The menu of the poorer classes in the Vizagapatam district is as follows:

Morning: 8 to 10 oz. of 'cold rice' together with the water in which the rice has been soaked overnight, a few grains of common salt and a little pickle (usually mango). 'Cold rice' is prepared by cooking the rice in the evening and allowing it to stand overnight in cold water.

Midday: ragi (millet) or *cholam* (a kind of maize) made into porridge: about 8 oz.

Night: cooked rice and 'tamarind water' with approximately 2 oz. of dried or fresh fish, if available.

In the Godaveri and Kistna districts rice takes the place in this dietary of *ragi* or *cholam* at the midday meal. Small amounts of mutton or dried fish are used by those who can afford to buy them but the extreme poverty of the masses makes these articles of food a luxury rarely indulged in. The non-Brahmins as a whole, and irrespective of their material prosperity, make very little use of *dhal* (either *arhar* or *mung*). The Brahmins, who are stated never to suffer from beri-beri, use *dhal* as a rule, and buttermilk or curds and *ghee* (clarified butter) regularly, while vegetable curry is one of the important items of their daily menu. It is obvious, therefore, that the margin of safety in the dietary of non-Brahmins of the poorer classes is, so far as its content of vitamin B is concerned, very small indeed.

Krishman has obtained the dietetic histories of twenty-five sufferers from beri-beri who were inmates of various hospitals in this district at the time of his inquiry. These may be taken as representative of the kind of diets with which beri-beri is associated in the Madras Presidency.

They show: (1) that the majority of these sufferers from beri-beri discarded the water in which their rice was washed; (2) that the disease occurred in the users of home-pounded rice in 6 out of 25 cases and that all of these washed the rice and discarded the washings; (3) that 2 of the cases supplemented the basal diet of rice with white bread; (4) that the average daily consumption of *dhal* was very low; (5) that 7 out of the 25 did not use *dhal* at all, and that 17 of the remainder only used it once every week or ten days and then in amounts which rarely exceeded 2 oz.; (6) that 8 out of 25 used fish, 2 of them daily and the other 6 once a week, in amounts rarely exceeding 2 oz.; (7) that 15 out of 25 used mutton, usually in amounts of 1 to 4 oz. a week, and in a few cases 1 to 2 oz. daily; (8) that 4 out of 25 used small quantities of buttermilk once a week or daily; (9) that 5 used coffee with a little milk and sugar daily; and (10) that all with one exception used 'tamarind water' to the amount of 8 to 10 oz. daily. 'Tamarind water' is a kind of soup made by boiling about 1 oz. of tamarinds in 20 oz. water. Chillies (½ oz.), pepper (1 oz.), salt (½ oz.), mustard and vegetable oil are added when boiling. Brahmins and other well-to-do people may add *dhal* and vegetables to this stock (2 and 4 oz. respectively), but the poorer classes cannot afford to do so. In no instance did *dhal* form more than 5 per cent of the total food intake; while the other food constituents (fish, mutton, vegetable, buttermilk, coffee, milk, sugar, tamarind water and pickles) were either very poor in vitamin B or were used in such small quantities as not to add greatly to the total vitamin value of the food. It can safely be said, therefore, that the food of these people was no richer in vitamin B than the beri-beri-producing diet described in XVIII, (3), consisting of polished rice and *dhal arhar*, the latter to the extent of approximately 8 per cent.

Two out of the twenty-five cases of beri-beri used a diet consisting of rice and *ragi* which did not differ appreciably in vitamin value from the two experimental and beri-beri-producing diets described in XIX, (2) and (3), made up of these two food grains.

XXVII. THE EXPERIMENTAL PREVENTION OF BERI-BERI IN MAN

For many years the prevalance of beri-beri in the Pagan Jail, Burma, has been a matter of concern to the authorities. No satisfactory explanation of its occurrence in this and not in other jails of Burma could be found; in all the dietary scale was stated to be the same (or the same on paper). This scale varied with the class of convict and with employment. It is as follows:

Rice	16 to 24 oz.
Dhal	2 ,, 4 ,,
Vegetables	5 ,, 10 ,,
Meat or fish (twice a month)	4 oz.
Condiments	½ to ¼ oz.
Oil (vegetable)	½ oz.
Salt	½ ,,
Tamarind	¼–0 oz.
Ngapi	½ ,,

The rice was purchased in bulk as paddy and was stored in cement godowns well protected from damp and vermin. From this store the rice was freshly prepared two or three days in advance of requirement. It was not deteriorated; nor was it devoid of pericarp. It was washed thrice, and the rice-washings were rejected. It was cooked in iron cauldrons.

The *dhal* was husked and washed before cooking. After boiling, the condiments fried in ground-nut oil were added together with salt and tamarind. The supply of vegetables was provided by the jail garden; in certain years it did not yield the required quantity and in these years beri-beri was most prevalent.

Judging from my observations on pigeons the capacity of the above diet to prevent beri-beri would depend largely on the vitamin value of the *dhal*. It appeared probable that the *dhal* might be of inferior quality and that after husking, washing and cooking the vitamin value of the original grain was likely to be considerably reduced. The *dhal* comprised approximately 7 to 10 per cent of the total food intake. In view of the fact that a diet of washed rice and *whole dhal arhar* will cause true beri-beri in 23 per cent of pigeons, when the *dhal* forms approximately 8 per cent of their total food intake, the dietary scale of this jail seemed to approach the danger level of vitamin insufficiency especially when allowance is made for individual difference in food intake and food assimilation and for environmental conditions. On such a diet beri-beri might well be precipitated in certain individuals under favourable conditions as by hard work, debilitating infections, exposure to cold and damp, and surface chilling of the body. Accordingly, I advised that one-half of the rice ration should be replaced by *atta* (whole-wheat flour) and that the convicts be supplied with abundance of root and green leafy vegetables; pointing out that in this jail the conditions of life appeared to be such that a more generous supply of vitamin B than that that sufficing for prisoners in more favourably situated jails, was indicated. This recommendation was adopted, with the result stated in the following extract of a report, dated 1st January 1927, from the jail superintendent to the Inspector-General of Prisons, Burma: 'The experiment, so far as I could judge, was satisfactory from the fact that not a single case of beri-beri occurred in this jail during 1926. From past experience the constitution of the prisoners, who were put upon the experimental test, was such that they would have been victims to the attacks of beri-beri during the cold season of this year but for the change in the diet of half-*atta* and half-rice with plenty of green leafy vegetables and root vegetables. Prisoners selected appear to like the new diet and their health is much improved in spite of their having had exposure to change in the climatic conditions, which was much greater than in previous years, as will be evidenced by the heaviest rainfall ever recorded (having occurred) during this year and especially during the latter part of the year. This change of diet has created such an impression among all prisoners in this jail that anyone who is not on the experimental list, whenever slightly indisposed, asked for the *atta* diet, which he thinks has more to do towards the cure than any other remedy.'

It follows, therefore, that the same measures which prevent *beri- beri columbarum* will also prevent *beri-beri hominum.*

XXVIII. CONCLUSIONS

(1) A condition—*beri-beri columbarum*—having all the pathological characters of human beri-beri has been produced under experimental

conditions in pigeons by means of diets of similar composition to those in use by human sufferers from the disease. This condition differs from *polyneuritis columbarum* in certain regards of which hypertrophy of the heart is the chief.

(2) The basal factor in the production of *beri-beri columbarum* is insufficiency, but not complete want, of vitamin B (or of the anti-neuritic fraction of this vitamin).

(3) There is an optimum degree of insufficiency of vitamin B at which *beri-beri columbarum* is most likely to arise; this optimum is provided by diets of which the vitamin-B value is from 20 to 50 per cent below the minimum required for the maintenance of normal metabolism.

(4) The ultimate cause of the disease is not the negative factor of vitamin insufficiency but a positive and toxic agent produced in the course of a disordered metabolism arising out of insufficiency of vitamin B in the food. The clinical and pathological manifestations of beri-beri are due in whole or in part to this specific agent.

(5) The existence of this agent has been demonstrated on pathological grounds and by statistical examination of the experimental data.

(6) *Beri-beri columbarum* and *beri-beri hominum* are preventable by the same means.

(7) Since *beri-beri columbarum* can be produced by diets of similar composition to those in use by the subjects of *beri-beri hominum*, since the pathological features of the two states are to all appearances the same, and since both are preventable by the same means, it is inferred that the aetiology of the two conditions is the same.

(8) Experiments on animals suggest that beri-beri-like maladies may be of different kinds: some due to infectious causes; some due to dietetic causes; and some due to a combination of both. The variety of 'beri-beri' dealt with in this memoir is due to dietetic causes; it is believed to be the variety which is endemic in certain parts of the Madras Presidency.

(9) The results of this investigation confirm the generally accepted view that endemic or true tropical beri-beri is due to insufficiency of vitamin B (or the anti-neuritic fraction of this vitamin) and not to toxic substances produced in rice by bacterial action. They do not preclude the possibility that other maladies included under the generic term 'beri-beri' may have a different aetiology.

XXIX. STATISTICAL EXAMINATION OF THE EXPERIMENTAL DATA RELATING TO THE HEART[1]

by E. R. SUNDARARAJAN, M.A.,
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The data available for statistical study consisted of the body-weights and heart-weights of the 348 control pigeons, and of the body-weights and heart-weights of the 552 polyneuritic birds; the remaining 396 were excluded.

The object of the statistical study was to ascertain the effect of the various deficient diets on the heart-weights; to demonstrate, by comparison with normal controls, the extent to which cardiac atrophy or cardiac hypertrophy had occurred in the 552 cases of polyneuritis; and to determine the influence of the various diets in producing one or other of these cardiac conditions.

The 348 controls, as compared with the 552 experimental pigeons, form a very good random sample, so that the heart-weights in the controls represent roughly the initial heart-weights of the experimental birds.

From this statistical survey the following conclusions may be drawn in regard to the 552 deficiently-fed and polyneuritic birds:

(1) The general effect of the deficient diets was to cause atrophy of the heart.

(2) A less common effect was hypertrophy of the heart.

(3) In some cases neither atrophy nor hypertrophy occurred.

(4) Exclusive diets of milled rice gave rise in about 70 per cent of cases to cardiac atrophy and in only about 10 per cent of cases to cardiac hypertrophy.

(5) Other diets—autoclaved mixed grains, washed parboiled rice, and rice and millet—gave rise invariably to a diseased condition of the heart in which hypertrophy occurred in about 25 per cent of cases; atrophy in about 50 per cent of cases; and neither marked atrophy nor marked hypertrophy in about 25 per cent of cases.

(6) The occurrence of so large a percentage of hypertrophied hearts, in pigeons fed on these 'other diets', clearly indicates the existence of a specific factor which counteracts the general tendency of the diets to cause cardiac atrophy, and produces cardiac hypertrophy in a considerable number of cases.

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[1] Mr. Sundararajan's statistical examination was undertaken at a stage of the investigations when the post-mortem records of 1,296 pigeons had accumulated. Following his study of this material a further 576 birds were used for experimental and control purposes.

CHAPTER V

Researches on 'Stone'

The Causation of Stone in India[1]

I. INTRODUCTION

Urinary calculus is very prevalent in India. From reports, for which I am indebted to civil surgeons, it appears that, during the years 1926–8, 34,325 persons were found to be suffering from the disease, or 1 in 10,000 of the population. These represent the combined records for three years, and relate only to persons seeking medical relief; but when it is remembered that hospital patients form but a relatively small fraction of the people of India, and that hospitals and dispensaries are but sparsely distributed, it may safely be assumed that the disease is more prevalent than these figures indicate.

The incidence of stone varies greatly in different parts of the peninsula: it is so prevalent in some localities that they are known as 'stone-areas', while in others it is rare or unknown. The prevalent belief that India in general is a land of 'stone' is erroneous: parts are, others are not. Thus, taking the above figures as our index of its prevalence, we find such variations as the following:

Cases per 100,000 *of Population*

In India generally	10
In Dera Ghazi Khan (Punjab)	438
In Hyderabad (Sind)	266
In Sukkur (Sind)	156
In Manipur (Assam)	84
In Dera Ismail Khan (N.W.F.P.)	62
In Saharanpur (U.P.)	25
In Ahmednagar (Lower Bombay)	13
In Benares (U.P.)	5
In Sylhet (Assam)	2·8
In Malabar (Madras)	0·3
In Kolaba (Lower Bombay)	0

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[1] Extract from number 140 in Bibliography.

Of the 34,325 sufferers from stone, 16,384, or approximately 1 in 20,000 of the population, had their stones removed at operation. I have taken this figure as my index of incidence and prepared a spot map. Each spot represents one stone removed at operation per 100,000 of the population of the particular district in which the patients lived. This map affords a fair indication of the distribution of the malady. The great 'stone-area' of India extends from Sind, the North-West Frontier Province, and the Punjab into the western parts of the United Provinces. As we pass eastward towards Bengal and Assam the prevalence of the disease gradually diminishes; similarly, it diminishes towards the south and south-east until in the southern parts of the Bombay Presidency, Mysore, Hyderabad, and Madras, the malady is relatively rare. It is relatively rare also in Burma. No reports were received from the greater part of Baluchistan, which abuts on Sind, and in which there is reason to believe the disease is also common; nor from Kathiawar, nor Travancore in the south. But these lacunae do not influence the general result, which, from the point of view of the investigator, is a significant one. It is that there are local factors which exercise a profound influence on the occurrence or non-occurrence of the malady. These influences may be geological, orographical, climatic, racial, nutritional, or microbic.

II. GEOLOGICAL INFLUENCES

Urinary calculus occurs for the most part on soils of the Post-Tertiary Period; indeed, a map of the geological features of India shows a great post-tertiary band extending eastward from the Kirthar, Sulaiman, and Hindu Khush Mountains on the west and north through the cultivated plains of sub-Himalayan India to Bengal and Assam; and comprising the great plains of the Indus, the Thar or Indian Desert, regions eastward of 'the five rivers' (Punjab), and the plains of the Ganges and its tributaries. It is in these plains that the great majority of all urinary calculi occur. At first sight one might be inclined to attribute significance to this association with Post-Tertiary rocks. But closer scrutiny of our data shows that no great importance can be attached to it, since it is in the plains of the Indus and not in those of the Ganges that the great majority of calculi occur.

III. OROGRAPHICAL INFLUENCES

While stone is most common in the plains of northern India, it is by no means confined to them. Far up in the mountain ranges of Dardistan, and throughout the Himalaya, one finds it also. In Chitral and Gilgit, in Gizar and Ishkoman, I have, in my early days, performed many operations for the relief of the condition—conscious even then of the temporary nature of the relief I was affording the sufferer. Stone is not related in any conspicuous way to the physical features of the country.

IV. CLIMATIC INFLUENCES

It is most frequent in the hot, arid, desert plains, where vegetation is relatively scanty; where grazing for cattle is poor, and scorched by the intense heat, or parched because of scanty rainfall. But its incidence is not always greater in these localities than in others more favourably situated. Thus it occurs with great intensity in the cultivated lands, watered by the five rivers of the Punjab or by the numerous Himalayan streams that go to swell the waters of the Ganges. Nor does rainfall appear to be a factor of importance: in Dera Ismail Khan (N.W.F.P.)—that furnace of the plains—where the rainfall is rarely more than 5 in. throughout the year, the incidence of stone is 62 per 100,000 of the population, as compared with 84 in Manipur (Assam), where the rainfall is 100 in., or thereabouts, and vegetation plentiful. One thing the western and eastern areas of the great stone belt have to some extent in common: a great disparity between summer and winter, and between day and night temperatures. But here again too much importance can be attached to this fact. It has been suggested that, because of the known effect of hypervitaminosis D in causing stone in rats, the constant exposure of a large part of the body to the rays of the tropical sun may induce in natives of India a condition of hypervitaminosis D, conducive to stone formation. Experiments on albino rats have not, in my hands, lent support to this view. Further, the exposure is greater in the loin-clad southerner than in the more completely clad northerner.

V. RACIAL INFLUENCES

It is stated in certain monographs on 'stone' that Mohammedans in India are more subject to it than Hindus; and it has been suggested that this is due to the Mussulman's habit of micturating in the squatting position, which renders complete evacuation of the bladder impossible. I have no data regarding the frequency of this habit in the two communities, though it would seem to be practised by both; but whether it be true or not that the Mussulman is more addicted to it than the Hindu, my data provide no evidence that stone is more common in the one community than in the other. In my series there are 1,024 cases in which particulars are given as to the community of the sufferer: of these, 757, or 73·9 per cent, were Hindus; 235, or 22·9 per cent, were Mohammedans; and 32, or 3·1 per cent, were in other communities.

Hindus form, approximately, 69·5 per cent of India's 320 million people; Mohammedans 21·3 per cent, and other communities 9·2 per cent—percentages which, so far as the two main communities are concerned, are practically identical with the percentage distribution of stone. Mohammedans are therefore no more subject to the malady than Hindus. If anything, other communities are more afflicted by it than either. The disease appears to be comparatively rare among Europeans in India; in my series they formed 0·44 per cent of the whole.

VI. NUTRITIONAL INFLUENCES

It is in the plains of the Indus, and in the sub-Himalayan regions fed by the upper reaches of the Ganges and its tributaries, that wheat is most grown. Here, too, the cultivation of maize is considerable; while in Sind the chief crop is millet. As we pass eastward along the Gangetic plain the cultivation of rice increases, reaching its acme in the Delta; southward, also, through Lower Bombay to Malabar and Madras, and south-eastward to the deltas of the Godaveri and Kistna rivers, the cultivation of rice increases. In Burma, too, rice is the principal, and often the only, cereal produced. In these places rice is the staple article of diet. The suspicion thus arose in my mind that the gradual decline in the incidence of stone, from regions where wheat is the principal cereal grown to those where rice is the chief crop, might be associated in some way with the cereal forming the staple article of diet of the people. Experiments on animals showed that this was so. Groups of young albino rats were fed on a diet of the same composition but in which the cereal, forming 90 per cent of the diet, differed. It was found that cereal foods ranged themselves in the following descending order of stone-producing potency: whole-wheat flour, oatmeal, north Indian millet (*bajra*), white flour, rice, and south Indian millet (*cambu*). The result of this experiment provided a partial explanation of the peculiar distribution of stone: its great frequency in the wheat-growing areas of the north-west, and its relative infrequency in the rice-growing areas of the south and east. But this association is not invariable. Thus stone is as common, even commoner, among the rice-eating Manipuris (Assam) as in the wheat-eaters of Dera Ismail Khan (N.W.F.P.). There is more in the occurrence of stone than the cereal which happens to be the staple food in this or that part of India: other dietetic factors are concerned. What these factors are has been revealed, in some part at least, by experiment on animals.

VII. EXPERIMENTAL PRODUCTION OF STONE

Well-fed albino rats do not suffer, certainly not in Coonoor, from stone; and these animals are very suitable for experimental work on this disease. I have used them throughout my own work. My first experiment was begun early in 1926. It lasted 157 days. Such experiments are tedious; the more so when one's object is to ascertain the faults in Indian dietaries to which 'stone' might be attributable. The diet used consisted of oatmeal 53 parts, linseed meal 20 parts, cornflour 25 parts, calcium phosphate 1 part, sodium chloride 1 part, and distilled water *ad libitum*. It may be wondered why I used oatmeal, since it does not enter to any considerable extent into the dietaries of the Indian people. I confess at once that chance determined my use of it—a lucky circumstance such as occasionally comes the way of the investigator, and for which he must ever be on the watch. The original object of the experiment was not to produce stone but to learn the effect on the thyroid gland of an iodine-poor diet such as this one was. But as things turned out the experiment taught me three things: (1) that the so-called iodine-poor diet did not cause thyroid enlargement; (2) that it did cause stone and its sequelae; and (3) that it also caused a very grave form of anaemia, which subsequent investigation in my laboratory by Dr. Lucy Wills showed to be due to *Bartonella muris* carried by the lice with which my rats were infested.

Here I may pause to draw attention to this last, and very instructive, result: an anaemia which is brought about in practically cent-per-cent of rats by removal of the spleen is also brought about by a faulty food deficient in certain vitamins. The intact spleen protects against this anaemia; and the conclusion is irresistible that the faulty food, by its action on the pulp cells of this organ, reduces its protective action against *Bartonella muris*. This is a very noteworthy instance of the effect of faulty nutrition in breaking down the defences of the body against infection.

But to return to stone. The above diet caused the disease in 21 out of 120 animals, an incidence of 17·5 per cent. In my next experiment one group of young rats was fed on the same diet as the above, and another on a diet wherein the oatmeal was replaced by whole-wheat flour. This experiment also lasted for many days, and when at length it was completed it revealed a significant difference in the incidence of stone in the two groups: of the 50 rats fed on the 'oatmeal diet' 4, or 8 per cent, had stone and its sequelae; of the 50 fed on the 'whole-wheat diet' 11, or 22 per cent, had stone and its sequelae. Whole-wheat flour was thus shown to be more potent to cause calculus than oatmeal. The next problem which naturally occurred to me was whether the other ingredients of the diet were also factors of importance: these ingredients were cornflour and linseed meal. A further tedious series of experiments was undertaken from which the knowledge emerged that neither of these food materials contained any positive or toxic agent which was concerned in stone production. It further emerged that diets composed exclusively of white flour or of white bread, either with or without added yeast or Marmite, were also capable of causing stone, though the stone-producing potency of white flour was markedly less than that of whole-wheat flour; vitamin-B deficiency was not concerned in causing stone. Subsequent experiments excluded another factor—deficiency of suitable protein.

Cereal foods thus appeared to vary in their stone-producing potency, and the experiment, mention of which I have made already, was undertaken to determine their relative degrees of potency. This experiment fixed them in the following descending order: whole-wheat flour, millet grown in the north of India, white flour, rice and millet grown in the south of India. The last did not cause 'stone' at all within the 515 days of the experiment. The significance of this observation in regard to the distribution of stone in India has already been referred to. Here another possibility arises: millet grown in one part of India may be stone-producing, while that grown in another may not: soil, manure, and irrigation conditions—which I had already shown to be capable of causing variations in the nutritive quality of food grains (McCarrison, 1926–8)—may thus be concerned in the production of stone. I have not so far been able to investigate this aspect of the matter.

The next step in my investigations was to see whether, by further additions to the stone-producing diet, the malady could be prevented. One group of rats was therefore fed on a diet of known stone-producing potency; another on the same diet to which whole milk was added, the milk being given in the proportion of two-thirds of an ounce per rat per day. Stone and its sequelae—cystitis, hydronephrosis, and pyonephrosis—were completely prevented by this measure. Clearly, therefore, milk contained 'something' which counteracted the stone-producing action of the diet. Further experiments of a like kind followed, but in these the substance added was butter or cod-liver oil, the action of which was compared with that of vegetable oils in common use in India. The butter prevented stone, so also did cod-liver oil; the vegetable oils did not. This narrowed the issue down to deficiency of vitamin-A-bearing ingredients as a chief food fault concerned in stone production.

By this time I had become acquainted with the original observations of Osborne and Mendel (1917), associating urinary calculus with deficiency of vitamin A in rats fed on synthetic diets, and with the later work of Fujimaki (1926), definitely demonstrating the specificity of vitamin-A deficiency in this regard. With this help my work proceeded more rapidly, but along the lines previously followed: the production of stone by means of foods in common use by the people of India.

It was stated in some of the reports which I received from civil surgeons, as well as in text-books on the subject, that hard waters have something to do with the causation of stone. Accordingly, lime was added to diets deficient, among other things, in vitamin A, with the result that the incidence of calculus, of cystitis, of hydronephrosis, and of pyonephrosis was greatly increased; and it was found that calcium-phosphorus imbalance was a further, and very important, factor concerned in the causation of certain types or urinary calculi.

The types of stones produced in these experiments were four: ammonium-magnesium-phosphate, calcium carbonate, calcium hydroxide, and stones composed of a mixture of calcium carbonate and calcium hydroxide.

My immediate object had thus been attained. It had been shown that certain food materials in common use by the people of India were capable of causing stone in rats when used in quantities disproportionate to certain other food materials that are antagonistic to stone formation.

VIII. INDIAN DIETARIES AND STONE

In India stone is a poor man's disease. Throughout the peninsula the staple article of diet of the people is one cereal grain or another. We have seen that these cereals vary in their stone-producing potency, and it may be assumed that all cereals contain, in some degree of concentration a positive agent or agents favourable to stone formation. This assumption is justified by the observation that the stone-producing potency of whole-wheat flour is greater than that of white flour—something favourable to stone production is in part removed from the whole wheat in the process of manufacturing white flour; this 'something' can scarcely be vitamin A, while we know it is not any of the other vitamins. (Here it may be suggested that the lesser potency of white flour as a stone-producing agent may be correlated with the gradual diminution of vesical calculus in England during the last fifty years—a period coinciding with the introduction and almost universal use of white flour.) We have seen also that the distribution of stone in India can be correlated with the kind of cereals in use in various parts of India; and we have seen, further, that milk and butter, if used in sufficient quantity, afford complete protection against stone in rats. Now the great fault of all Indian dietaries among the poorer classes, who are the chief victims of stone, is that their diets do not contain anything like enough milk and milk products, and I postulate that according to the kind and quality of the cereal grain they use as the staple of their dietaries, and according to the poverty of these dietaries in milk and the products of milk, so they will be more or less likely to suffer from stone. Milk and the products of milk are among the greatest of India's needs at the present time. I do not contend that this is the whole story; indeed, I know it is not, but it represents certain chapters of it.

IX. DIETETIC FACTORS CAUSING STONE

There appear, therefore, to be two categories of dietetic factors concerned in stone formation: (a) positive factors, including excess of lime in the diet, and some unknown agent present in whole cereal grains; and (b) negative factors, including deficiency of vitamin A derived from animal sources, and deficiency of phosphates relative to the amount of lime in the diet. I say 'vitamin A derived from animal sources' because millions of people in India are dependent for their supply of this factor —whatever that factor implies—on vegetables; I am not yet certain that the latter source of vitamin A is, from the point of view of stone prevention, as good as the former. I do not think it is, and I notice that de Langen (1929) of the Dutch Indies is of a like opinion.

Here it is necessary to make my position clear in regard to the value of whole-wheat flour and oatmeal as articles of diet. Because I have found that whole-wheat flour and oatmeal, when they compose the major part of an imbalanced diet, are stone-producing, this is not to say that I desire to displace these two most valuable foods from the high place in the dietaries of mankind to which they have attained throughout the centuries. To do so would be to doubt the evidence of one's own eyes, and to fly in the face of reason. Who that has seen the magnificent physique of the Sikh or Pathan would dare to recommend them to change their staple diet of unleavened whole-wheat bread for the white loaf of commerce? And who that has seen the slum children at Miss Margaret McMillan's 'Nursery School' at Deptford can doubt that she was right to exercise the care she did in the selection of the oatmeal on which experience had taught her to rely as a constituent of her children's dietaries—children who rarely need the dentist? The truth is that no single food material is in itself a 'complete food'—even milk is not; if it be not faulty in one regard it is faulty in another. The best are those whose faults are least; and in the latter category both wholewheat flour and oatmeal are to be included. Milk, as an exclusive food, will cause anaemia in rats; onions, anaemia in dogs; cabbage, goitre in rabbits; and oatmeal or *atta* will cause stone in rats; yet what better food can there be for mankind than a judicious mixture of all four? Animal experimentation has its uses—its great uses—but like every other instrument employed by man the results of its use must be judged by reason and experience.

X. STONE: A DISEASE OF FAULTY NUTRITION

During the course of my experimental work I have produced stone in 250 animals. The young rats that I have used have always been about a month old at the outset of the experiments: that is to say, of an age at which they are able to fend for themselves, and are no longer dependent on maternal nutriment. They would correspond approximately to children or a year of two old. I have grouped these cases together in a chart. In rats 'stone' is a disease of early life; the pinnacle of age incidence is reached when they are about 120 days old, when they have been living on the stone-producing diets for about 90 days. Thereafter the curve of age incidence declines rapidly and gradually fades away, until, at the age of 400 days or over, stone is relatively rare. Now compare this curve, first with that of the age distribution of stone in India. The same rapid rise will be noticed during its earlier stages, the same rapid fall and its gradual fading away thereafter; the curves in the rat and in the Indian are practically identical. Taking these facts into consideration with those I have already presented, the conclusions seem to me to be irresistible that in India urinary calculus is a disease of faulty nutrition, and that the same food faults which produce the malady in rats procuce it also in the people of India.

But it is not always so. In my next illustration set out in the same diagram the percentage incidence of stone at each age period as it is found in India, in France, in the United States of America, and in England. Here the incidence curves are of orders so different as forcibly to suggest that while the chief causes of stone in India and in France are probably the same—nutritional in the main—those in England and the United States of America are in the main different: in the one the high peak of incidence is at the earlier period of life, when nutritional disturbances are most likely to be felt; in the other it is at the other end of life. Many factors may account for stone production in later life: stone formed in early life may be endured to later life: stagnation of urine due to enlarged prostate and the like may cause it, or infection. But it is not my purpose to discuss the causation of stone in later life—a condition relatively rare in India.

XI. SEX INCIDENCE OF STONE

In India stone is much commoner in males than in females: in my series the proportion is as 13·2 to 1. In children under the age of 15 years, 92·5 per cent of stones occurred in males. My observations in this regard are in conformity with those of Winsbury White (1929)—in fact his curve and my own are practically identical; and if I be correct in my contention that in Indian children stone is a disease of faulty nutrition it is very likely to be so also in English children. One point of interest is brought out in my diagram: the Indian curve shows that very occasionally stone may occur in breast-fed infants.

The greater incidence of stone in males does not apply to experimentally produced stone in rats. In these animals it is slightly more common in females. I have, at present, no explanation to offer of this difference in the two species.

XII. INCIDENCE OF RENAL CALCULUS IN INDIA

In comparison with vesical calculus, renal calculus is relatively rare in India. In a series of 454 cases of stone recently sent to me by surgeons practising in parts of India where the disease is common, there were only 34 renal stones; a proportion of vesical to renal of 13·5 to 1. Whereas vesical calculus is pre-eminently a disease of early life, renal calculus is a disease of middle life. In the course of my experimental work I have had frequent examples of renal calculus in rats. In my series of 250 experimentally produced stones there were 31 renal calculi, a proportion of vesical to renal of 8 to 1. In albino rats renal stone is equally common in the two sexes. In human beings it is much commoner in males.

XIII. INCIDENCE OF URETERAL STONE IN INDIA

Ureteral stone is rare in India, or it is rarely operated upon. Among the 16,384 calculi removed during the years 1926–8 there were only 14 ureteral stones. A diagnosis of stone in the ureter was made in other cases, but the patients refused operation.

In my series of 250 experimentally produced stones in rats there were 21 examples of ureteral calculus: in the majority of these the stone was obviously on its way from the kidney to the bladder, and was not impacted in the ureter. Males had such ureteral stones more often than females (16 to 5).

XIV. CYSTITIS, INCRUSTED CYSTITIS, PYONEPHROSIS, ETC.

It is not possible, in the time at my disposal, to do more than mention the morbid states of the urinary tract so often associated with stone in experimental animals: cystitis, incrusted cystitis, hydronephrosis, and pyonephrosis. Any of these may occur without stone formation, though such occurrence is the exception and not the rule. We do not, as yet, know why one animal develops stone while another fed on the same diet develops incrusted cystitis or pyonephrosis without stone. Cystitis is not a necessary precursor of stone, even when the stone is of the ammonium-magnesium-phosphate variety. And cystitis without stone can be produced in rats with considerable certainty by diets deficient in vitamin A but containing an excess of animal protein—a combination of food faults not uncommon in human sufferers from cystitis. Curiously enough the cystitis so produced is commoner in female than in male rats: I believe I am right in saying that in human beings cystitis is also commoner in the female sex.

XV. CHEMICAL COMPOSITION OF HUMAN STONES

During the past three years analyses of 226 human urinary calculi have been made in my laboratory (Newcomb and Ranganathan). The stones may be classified according to their chemical composition as follows:

	Number	*Percentage of Total Number of Stones*
Pure uric acid	15	6·63
Pure oxalate	13	5·75
Pure phosphate	3	1·32
Phosphate-oxalate	23	10·17
Urate-phosphate	20	8·85
Urate-oxalate	78	34·51
Urate-oxalate-phosphate	74	32·74
Total	226	99·97

According to Kahn (quoted by Kauffmann) (1929), pure uric-acid calculi are rare: they formed 6·6 per cent of the total in our series of 226. Freyer (1908) found that most of the stones containing uric acid or urates occurred in young people. Our data do not confirm this observation. He also found that 64 per cent of his Indian stones contained either uric acid or urates; our figure is higher, 82 per cent. He noted also that calcium-oxalate calculi were commoner in adults than in children: in our series the average age of sufferers from pure oxalate stones was 29 years. Pfister has called attention to the predominance of oxalate stones in Egypt and in India; in our series of 226 there were 13 pure oxalate stones (5·75 per cent), while 83·17 per cent contained more or less oxalate.

Our analyses of kidney stones are relatively few, but they show that in India these stones consist mostly of calcium oxalate and not of uric acid or urates: an observation in conformity with that of Benjamin Moore (1911) and of Rosenbloom (1915); and in opposition to that of Stengel and Fox (1927). It would seem from the literature on this subject that renal calculi are generally considered to be composed of uric acid: this is not our experience in India.

Much difference of opinion exists as to the chemical composition of the nuclei of stones. It is not always easy to find the nucleus of a stone, or, when one has found it, to be sure that one is dealing only with the nucleus. One of my assistants (Mr. Ranganathan, 1930) has recently gone into the matter in some detail. He found that uric acid or urates formed the chief constituents of the nuclei, phosphates occurring only in traces; and that the composition of the nuclei did not always run parallel with that of the stones containing them, though an approximate parallelism existed in some cases.

There is a general belief that it is possible, from the physical characters of a stone, to make a good guess at its chemical composition. We do not find that this is so; such guesses are in general very inaccurate (Newcomb and Ranganathan, 1930).

So far as our analyses of human stones go, it would seem that no particular kind of stone is more prevalent in one part of India than another. We have not found it possible, from the incomplete dietetic histories of sufferers, to correlate the chemical composition of calculi with that of the diets eaten by the people from whom they were removed: the great majority of their dietaries had, however, one fault in common—insufficiency of vitamin-A-bearing ingredients.

XVI. CHEMICAL COMPOSITIONS OF RAT STONES

As previously stated, the stones produced in rats were of four varieties: ammonium-magnesium-phosphate, calcium carbonate, calcium hydroxide, and a mixture of the last two. The essential difference between them and human stones is the complete absence of uric acid or urates. Excluding traces of urates (forming less than 5 per cent of the total ingredients) uric acid or urates occur in 82 per cent of all human stones in India. The usual explanation given for the absence of uric acid in rat stones (as well as in those of cattle) is that these animals possess the power to oxidize approximately 80 per cent of the circulating purines to allantoin. Allantoin is several times more soluble in water than is uric acid, and hence it never forms a constituent either of rat or of cattle stones. Human beings do not possess this power, and in them the degradation of purine bodies stops short at uric acid; and, as uric acid is very sparingly soluble in water, it is almost always found to be a constituent of urinary calculi in man (Swift Joly).

XVII. POWER OF THE URINE TO RETAIN URIC ACID IN SOLUTION

Urine varies greatly in its power to dissolve uric acid and retain it in solution. We have recently found that the urine of rats fed on purely vegetable diets retains much more uric acid in solution than that of animals fed on diets containing large amounts of animal protein. Hindhede has, I believe, made a similar observation in man. The urine of rats fed on a diet of liver was capable of dissolving only a very little uric acid, and this was thrown out of solution after standing for twenty-four hours. The composition of the diet, by influencing the capacity of urine to hold uric acid in solution, may thus have a bearing on stone formation.

XVIII. CHEMICAL COMPOSITION OF CATTLE STONES

Cattle stones, as we find them in India, are usually small, round, shot-like bodies, having, when fresh, a light or deep golden-yellow sheen. They may occur in large numbers in the same animal, and their usual location is the urethra. They are made up of thin layers, like the coats of an onion, all layers being of the same composition. Stones occurring in the kidney in cattle do not possess these physical characters; they are usually single, larger, of irregular shape, and are devoid of metallic sheen. But whether occurring in the kidney or in other parts of the urinary tract their chemical composition is, with rare exceptions, the same. Analyses have been made of twenty-four cattle stones in my laboratory (Ranganathan, 1931). Their composition has been found to be fairly uniform: calcium carbonate with a little magnesium, the latter presumably also existing as carbonate. In only one of the twenty-four stones was this composition departed from. In this case (a calf) the stone had a relatively high moisture content, a high nitrogen, phosphate, and magnesium content, and a low calcium content; carbonates were not present.

We have been fortunate in being able to reproduce not only the chemical but the physical (excepting the metallic sheen) characters of cattle stones under experimental conditions in albino rats Briefly, this is how it is done. The rats were fed on a diet deficient in vitamin A and containing an excess of lime relative to the amount of phosphate in the diet (McCarrison, 1931). By keeping them on this diet for seventy to eighty days, and then supplying the missing vitamin A (in the form of radiostoleum) it was found that of those that survived the process a high percentage had stones of composition and physical characters closely resembling those of cattle stones. Apparently what happens is this: During the first, or vitamin-starvation, period a mass of calcium carbonate debris is deposited in the urinary tract. On supplying vitamin A, but allowing the calcium-phosphate imbalance to remain, the whole (if it be small) or part (if it be large) of the calcium carbonate deposited during the first period is redissolved and dispersed. But in some cases parts remain as isolated collections or grains; and during the second period of the experiment, when vitamin A is provided, these act as foreign bodies, and a layer or layers of calcium carbonate is deposited around them. This is at present a working hypothesis; but we hope by hitting off just the right diet to keep the rats alive long enough, and by alternating the periods of vitamin want and of vitamin supply with sufficient nicety, while retaining the calcium-phosphate imbalance, to reproduce these cattle stones with still greater exactitude.

In chemical composition the stones experimentally produced in rats were identical with the calcium carbonate stones found in Indian cattle (McCarrison, 1931).

Through the kindness of Mr. Hilson, Director of Agriculture, Madras, I have been able to secure reliable information regarding the food of the cattle in parts of the Madras Presidency where cattle stone is prevalent. They are fed on maize, millet, or rice straw, the husks of ground-nuts, and the empty pods of legumes. All these fodders are poor in phosphates and disproportionately rich in lime: ground-nut husks, for instance, contain as much as 3·78 per cent of CaO and only 0·36 per cent of P_2O_5. After the rains the cattle obtain much more green fodder, and with it a much-needed supply of vitamin A. Periods of vitamin want alternate with periods of vitamin supply, the diet remaining all the while imbalanced with respect to calcium and phosphates. It is notable that the only exception to the rule that cattle stones are composed of calcium carbonate was in a calf, aged 6 months, which, after weaning, was fed on a diet in which calcium-phosphate imbalance was not marked. Strong support is thus lent to the hypothesis above mentioned as to the manner of calcium-carbonate-stone formation. Our investigations have shown, further, that in the formation of these stones the calcium-phosphate imbalance is even more important than the vitamin-A deficiency (Ranganathan, 1931). We find that the incidence of such stones can be very greatly reduced in rats by adding to the vitamin-A-poor and lime-rich diet an amount of sodium phosphate sufficient to form, with the excess of lime, insoluble calcium phosphate in the bowel. The further addition of vitamin A completely prevents the disease. I may therefore claim with some reason that the problem of 'cattle stone' in India has been solved so far as the laboratory can solve it.

XIX. FUNCTION OF VITAMIN A IN THE PREVENTION OF STONE

In my last lecture I referred at some length to the effects of vitamin-A-deficient diets on epithelial structures throughout the body. No tissue suffers more severely from want of this vitamin than that of the urinary tract. It seems to me very probable that desquamated, keratinized epithelium from this tract may form the nidus round which calculus deposition occurs. It is true that in rats infection, as a rule, rapidly supervenes; and this, no doubt, may be in part responsible for the chemical composition of one variety of rat stone—the ammonium-magnesium-phosphate variety. But although naked-eye evidence of infection is the rule, exceptions occur in which this variety of stone is found without any obvious cystitis. Further, cystitis is no less common in rats suffering from calcium-carbonate stones, and in these ammonium-magnesium-phosphate is conspicuous by its absence.

In my experiments I have found that the volume of urine excreted depends to a great extent on the presence or absence of vitamin-A-bearing ingredients in the diet; when absent or small in amount the volume of urine is low; when present in sufficient quantity it is normal or high. Sodium phosphate has also a very marked effect in this regard, greatly increasing the urinary excretion. It is significant that associated with the addition of vitamin-A-bearing substances (whole milk, cod-liver oil, or radiostoleum) to stone-producing diets, and of these substances and sodium phosphates to such diets containing an excess of lime, the urinary excretion from being scanty becomes copious, and at the same time stone is prevented.

There is, of course, another direction in which vitamin A acts in the prevention, and its deficiency in the causation, of stone. I refer to its power to prevent infection of the urinary tract, and to the influence of its deficiency in favouring such infection. This brings me to the last of the influences which may determine the occurrence and distribution of stone in India—infection.

XX. INFECTIOUS INFLUENCES

The work of Rosenow and his colleagues of the Mayo Foundation is, no doubt, familiar: his experimental production of gall-stones in animals by infection with streptococci from cases of cholecystitis in man; and, more recently, his production of urinary calculi by the devitalization and infection of teeth in dogs with streptococci from cases of nephrolithiasis. Rosenow's procedure is, first, to produce 'septic foci', using, for the disease he wants to produce, streptococci obtained from a case of the particular disease in man. He finds the coccus to be specific: that from cholecystitis will produce gall-stones; that from nephrolithiasis, urinary calculus. This sequence of events is probably the same in essentials as that occurring in rats: in these, foci of devitalization are produced in the urinary tract by the defective diet, and, in some forms of stone at least, chance infection may do the rest. But the point of special interest to India in Rosenow's work is that a specific kind of infection may, as he and Meisser suggest, be associated with stone, and thus account for the prevelence of the disease in certain localities. Personally, I am quite prepared to believe that this may, to a limited extent, be so; for although I have shown that the distribution of stone in India may, in some part, be accounted for by the kind of cereal used by people whose diets contain an insufficiency of vitamin-A-bearing ingredients, this is not the whole story, nor does it explain the occurrence of stone in all localities in India or in all individuals. Bilharzia, though a frequent cause of stone in Egypt, does not appear to be so in India; and in infection by bilharzia malnutrition is a potent favouring influence.

XXI. MECHANISM OF STONE PRODUCTION

This lecture has dealt with the causation of stone, not with the mechanism of calculus deposition. My researches have been mainly of the practical kind: my business being to tell the people of India how they can themselves avoid stone and prevent it in their cattle. It matters little to them, though it is of great interest to the medical scientist, whether the deposition of stone can be most satisfactorily accounted for by faulty metabolism dueto dietetic causes, by infection, or by physico-chemical disturbances in the urinary tract. I have little doubt that both faulty food and infection may induce the physico-chemical disturbances responsible for stone deposition; but I know that a properly constituted diet will go a long way to prevent both infection and physico-chemical disturbances. It seems to me that all three agents—dietetic, infectious, and physico-chemical—play their part in the genesis of stone, and in designing its architecture; on occasion, and in certain individuals or in certain places, the star part may be taken by one or by the other. In India the star part is taken by diet.

The President and Council of the College have signally honoured me by their invitation to tell something of my research activities in India, and I have been deeply conscious of the responsibility this honour has imposed upon me. I have purposely chosen to refer only to those of my activities which I have thought might be of special interest to surgeons. Even with this limitation much has had to be omitted or passed by with but a few words. But if what I have said may serve to indicate directions in which the newer knowledge of nutrition touches upon the Art of Surgery—to indicate lines of investigation which hold out the prospect of the solution of certain surgical problems—then I shall have fulfilled, in some small measure, the duty imposed upon me by the invitation to address this great College.

CHAPTER VI

Researches on Human Diets in Relation to Health and Disease

Memorandum on Malnutrition as a Cause of Physical Inefficiency and Ill-Health Among the Masses in India[1]

The object of this memorandum is to indicate (a) the great importance of malnutrition as a cause of physical inefficiency and ill-health among the masses in India; (b) the intimate connection which exists between problems of nutrition and those of agriculture; and (c) the necessity for the closer co-ordination of nutritional, medical, veterinary and agricultural research in this country.

Of all the disabilities from which the masses in India suffer, malnutrition is perhaps the chief. The more spectacular, endemic and epidemic diseases, such as cholera, malaria, dysentery, tuberculosis and leprosy, kill their thousands yearly; but malnutrition maims its millions, and is the means whereby the soil of the human body is made ready for the rank growth of the pathogenic agents of many of those diseases which afflict the Indian people. It has, for example, been shown by researches carried out under the auspices of the Indian Research Fund Association, that dysentery—a common scourge of India—can be produced under experimental conditions in animals, closely related to man, merely by feeding them on food deficient in certain substances (vitamins) upon which normal metabolism is dependent. It was found that while well-fed animals might harbour the *entamoeba histolytica*, which is a cause of dysentery, they did not develop this malady although living in the same room and subject to the same risks of infection as ill-fed animals which, being carriers of this organism at the time the experiment commenced, developed dysentery in consequence of the lack of resistance to it brought about by the defective food. Similarly, it has been shown that hog-cholera and other infections can be caused to overrun the animal organism by the same means. These observations have now been confirmed and extended in other countries; and quite recently it has been found that the susceptibility to tuberculosis, typhoid

[1] Extract from number 119 in Bibliography.

fever and pneumonia—all of which are very prevalent in India—is greatly enhanced by the use of food of low biological value which contains an inadequate supply of vitamin A. Investigations of this kind have made it possible to enunciate the rule that many pathogenic agents of disease are capable of exercising their harmful effects only when the human or animal body is debilitated by various means of which imperfect nutrition is the chief. It follows, therefore, that a primary essential in the prevention of such diseases is the adequate nourishment of the human and animal organism. A number of other diseases of a metabolic nature are likewise the result of improper food. Of these it is only necessary to mention scurvy, rickets, beri-beri, certain eye diseases and stone in the bladder, all of which exact an enormous toll in this country.

The effect of imperfect food in causing a degree of physical inefficiency, which may not be associated with any gross evidence of disease, is exemplified in India as in few other countries in the world. Few who have travelled far in India can have failed to observe the remarkable difference in physical efficiency of different Indian races; and although there are a number of factors, climatic and other, which play their part in determining these differences, yet it has been shown by researches carried out in this laboratory, and by Colonel McCay in Calcutta, that nutrition is the chief among them. The differences in physical efficiency of different races in India have been definitely correlated with differences in the biological value of foods which necessity, habit, or religious prejudice has forced them to use.

Malnutrition is thus the most far-reaching of the causes of disease in India. It is one of the greatest—if not *the* greatest—problems with which the investigator of disease is faced. It is, too, the chief among the problems facing those engaged in agricultural research. The ultimate aim of both is the same: the adequate nutrition of the people. So far, then, from agricultural and nutritional research being carried out in isolated compartments, there should be the closest co-operation between them, to the mutual advantage of each and to the widening of scientific vision.

It is not alone in regard to the human subject that malnutrition exerts such harmful effects. Man's domestic animals suffer no less than he himself. It suffices in this connection to refer to the effect on cattle of pasturage which is deficient in certain mineral ingredients. As an example of this kind the now well-known effect of deficiency of phosphorus in the soil, and, therefore, in the vegetation, on the health of cattle and sheep may be mentioned. Such deficiencies exist in large tracts throughout India as, for instance, in the soils of Bihar. In India, unfortunately, millions of stock exist in a state of semi-starvation. As draught animals they are consequently inefficient: and as producers of milk and milk products—so essential as food for mankind—they are more inefficient still.

There is, perhaps, no more important department of agricultural and nutritional research than that which deals with animal husbandry; and here I should like to emphasize that the problems of animal husbandry are also the problems of human husbandry.

Human and animal inefficiency is reflected in the soil; in its imperfect cultivation; in inadequate manuring; and in crops scanty as to quantity and deficient as to quality. Too few animals are kept by the cultivator, as the scanty vegetation cannot support them; and so there is returned to the land too little of that organic matter, in the form of farmyard manure, on which the continued fertility of the soil is so dependent. It has been shown in regard to plants, as in regard to animals, that they cannot thrive, nor their seed attain to the fullest 'reproductive quality', unless they be provided, in addition to the mineral constituents of their food, with certain organic substances known as 'auximones'. These substances, which are akin to vitamins, are as essential to the normal metabolism of plants as vitamins are to the normal metabolism of man and animals. They not only enable the plant to build up from the simple ingredients derived from the soil those organic complexes required as food by men and animals, but they enable it to elaborate vitamins without which these organic complexes cannot be properly utilized by the animal organism. Auximones are produced in the soil from decaying organic matter by the action of certain soil bacteria; and the best organic matter for this purpose is farm-yard manure. So it is that such disabilities of mankind as are due to faulty nutrition are sometimes traceable to the soil itself, which has become exhausted and unproductive of the best kind of food through improper attention and cultivation. Malnutrition, thus, pursues its harmful course in an ever-widening vicious circle; the cultivator is too often ill-nourished and ravaged by disease which is commonly the result of his ill-nourishment; his beasts are alike ill-nourished; while both toil wearily in a heartless effort to extract from the ill-nourished earth enough to keep them from starvation. The solution of the problem of malnutrition is thus, to a great extent, one of improvement in methods of agriculture.

Considerations of this kind led me, in the course of the inquiry on which I am engaged, to attempt, in a way as wide as my limited circumstances permitted, a study of the soil conditions which influence the nutritive value of the commoner food grains of India. Millions of people in this country rely from generation to generation on a single cereal as the main staple of their dietary. It seemed necessary, therefore, to be aware not only of those soil conditions which influence the yield of grains but of those which influence their nutritive quality. This attempt was made not only because it was the logical outcome of the work on which I was engaged—an inquiry into the effect of faulty food on the causation of disease in general—but also with the object of widening the scope of nutritional investigations and of linking them up with agricultural research to which they are so closely allied. The soil conditions which it was thought would be likely to influence the nutritive quality of food grains were (a) the chemical composition of the soil itself; (b) the manurial treatment to which it is subjected; and (c) irrigation as compared with normal rainfall. So far my investigations have not proceeded beyond the experimental study of the effect of certain manures on the nutritive value of millet and wheat. They are, unfortunately, very tedious and the output of work is limited by the limitations of a single investigator. The results already arrived at are, however, of interest. It has been found in regard to millet—a common food grain in south India—that soil on which it is repeatedly grown, but which has received no manure for many years, yields a grain the nutritive value of which is so low that it may actually be harmful to the users of it; suggesting the acquirement by the grain of toxic qualities. It has been shown, moreover, that the nutritive and vitamin values of the millet grown on soil treated with cattle or farm-yard manure are markedly superior to those of millet grown on the same soil when treated with a complete chemical manure. In regard to wheat, it has been found that when it is grown on soil treated with farm-yard manure, its nutritive value is approximately 17 per cent higher than when grown on soil treated with complete chemical manure. The deficiencies of the wheat grown under the latter conditions are due in the main to an inferior content of vitamin A, that substance which is so essential in maintaining the resistance of man and his domestic animals to infectious diseases. In this work—which I venture to think provides an example of the advantages to be derived from collaboration between investigators of nutritional and agricultural problems—I have had the active assistance of the Department of Agriculture, Government of Madras, and of the Agricultural Chemists on the staff of the Agricultural College, Coimbatore, without which it would have been impossible to carry it out.

Questions of irrigation—the means to be adopted to prevent the slow but sure deterioration of soil which is constantly being irrigated, and the consequent deterioration of the crops grown upon it—are alike of interest to students of nutrition and public health and to those engaged in agricultural research. The possible bearing of these questions on the tendency towards intense malaria when dry crops are grown under canal irrigation is one of the most important of the public health problems awaiting solution. It has been referred to in detail in Mr. Albert Howard's Presidential Address before the Indian Science Congress at Bombay early in the present year: an address which brought into prominence certain aspects of agriculture and their relation to disease which are of the utmost importance to this country.

Among the manifold needs of India at the present time not the least urgent are these:

(a) The wise extension of research on nutrition—plant nutrition, animal nutrition and human nutrition—under broad-minded direction. These are not different subjects but the same subject: a continued story following a natural and ordered sequence from its beginning with the soil, through vegetable and animal life, to its final stage in man himself. In the telling of this story India should be encouraged to play an adequate part. My experience of Indian assistants has taught me that nutritional research is of a kind which appeals to the Indian possessed of the necessary scientific education. For my own part, I would desire to see many such young Indians trained in its prosecution and engaged upon it under proper direction.

(b) A second need is the co-ordination of all the forms of research—nutritional, medical, veterinary and agricultural—which have for their aim the betterment of the health and physical efficiency of the people of India. It is essential that those who are engaged in agricultural research should be aware of its bearings on public health or vice versa. At the present time much effort is dissipated for want of such co-operation between research workers. The matter is, however, beset with many difficulties. I mention it merely to indicate its importance.

It is, I believe, only by the extension of research along broad lines, by its proper co-ordination, and by the employment of the best brains which India can herself provide, that this country will obtain the highest return for money expended upon research.

Problems of Nutrition in India[1]

Throughout the whole of India the staple article of diet of the masses is a cereal grain of one kind or another—wheat, barley, millet, maize, rice—sometimes a mixture of two or more of them. Most of these grains are eaten whole; these are not subjected to any milling or refining process before use. The outer layers of the grain and embryo, containing valuable dietary constituents, are thus consumed with the endosperm. Rice is the single exception to this rule; though within recent years [written 1932] the use of white flour and white bread is spreading in the larger towns and cities. Rice is always subjected to some form of refining process. In country districts, distant from rice-mills, it is pounded by the villagers in large mortars; a process which removes some, but not all, of the external layers. In towns it is milled and polished in the raw state or after parboiling or curing. As is well known these processes reduce its nutritive value to a greater or a lesser degree.

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[1] Extract from number 126 in Bibliography.

Biological tests in this laboratory have shown that these cereals differ in nutritive value; whole wheat being the most, and whole rice the least, nutritious. The other cereals occupy an intermediate position between these two extremes. All are deficient in certain food essentials—suitable protein, calcium, sodium, iron, phosphorus and certain vitamins. These deficiencies are greatest in whole rice; and, as rice is always subjected to refining processes, always washed before cooking, and always consumed after prolonged boiling, this cereal is, generally speaking, of much lower nutritive value than any of the others.

The nutritive value of some of these cereals may, and often does, vary in different localities: amongst rices grown in different parts of India this variation may be considerable; the same is true of millets. Thus certain millets grown in the south of India have been found to be surprisingly low in vitamin B—an observation which has a bearing on the not infrequent occurrence of beri-beri in millet-eaters resident in endemic areas of this disease. It has been found, too, that ground-nuts and split peas (*dhal*), grown in certain localities in south India, are unexpectedly low in this factor. Observations of this kind have led to the suspicion that the nutritive value of certain cereal grains, legumes and nuts, in common use in India, may depend to some extent on the conditions of soil, manure and irrigation, under which they are grown. A considerable amount of evidence in support of this supposition has been obtained in this laboratory. Thus, it seems certain that rice grown under conditions of natural rainfall, or of watering designed to simulate natural rainfall, contains more vitamin B than the same rice when grown in standing water. The former practice is generally followed in the south-west of India where beri-beri is not endemic; the latter in the south-east, where it is. Biological tests appear also to indicate that manurial conditions influence the nutritive value of cereal grains; and it seems likely that the almost universal practice of utilizing cow-dung for fuel purposes, instead of returning it, as manure, to the soil, is one that has a bearing on the nutritive value of Indian food crops. Thus, agricultural practice appears to have a definite relation to problems of nutrition in this country.

The varied conditions of climate, rainfall, irrigation and soil prevailing throughout the Indian Peninsula make some part of it more suited to the cultivation of one cereal than of another. The cereal or cereals grown in any particular locality are those that enter into the dietaries of the inhabitants of that locality. In the north of India—North-West Frontier Provinces, Punjab, Baluchistan and United Provinces—wheat is the principal cereal grown; though some rice, barley, maize or millet is also grown. Generally speaking, the races resident in these areas—Pathans (Afridis, Waziris, Bajauris), Punjabis, Sikhs, Baluchis, Rajputs and Paharis—are wheat-eaters. Wheat is the staple article of their dietaries; the other cereals mentioned being merely adjuncts to it. A large amount of wheat is also grown in parts of Central India, Bombay and the Deccan; but in general the races resident in these localities, such as the Maharattas, use a diet of mixed cereals—usually wheat and rice. Towards the east, through Bihar to the coast of Bengal, all down the east and west coasts and throughout the Madras Presidency rice is the principal cereal grown; though in parts of these regions millet is also a considerable crop. But, for the most part, the races resident in these areas are rice-eaters. Throughout the rest of India millet is the chief crop, and forms the staple article of diet of races—such as the Kanarese—resident therein, who commonly use rice as a supplement to it. In parts of Travancore the staple article of diet is the tapioca root supplemented with rice.

As we pass from the north to the east, south-east, south-west and south of India, there is thus a gradual fall in the nutritive value of the cereal grains forming the staples of the national diets, this fall reaching its lowest limit amongst the rice-eaters of the east and south. There is also a gradual fall in the amount of animal protein, animal fats, and vitamins entering into these diets. The races of the north are either milk-users or meat-eaters or both; while those of the south and east use both meat and milk sparingly and sometimes not at all. Thus, the Pathans are meat-eaters; the flesh and fat of sheep and goats forming a principal constituent of their dietaries. They also use milk freely, chiefly in the form of buttermilk, curds and butter or *ghee*. The Sikhs are large users of milk and the products of milk; meat being only an occasional addition to their diet. The Maharattas also make free use of milk and milk products; an additional source of animal protein being eggs and fish. The Bengalis, Kanarese and Madrassis, on the other hand, are for the most part vegetarians; and although some of them do eat mutton or fish, millions do not, while milk and milk products are, in general, less extensively used by them than by northern races. It so happens, therefore, that as the nutritive values of the cereal grains diminish there is also a diminution in the amount of animal protein ingested and in the level of protein metabolism attained by the races concerned. There is, too, a precipitate fall in the amount of vitamins A and B ingested by the races of the south as compared with those of the north. Legumes (*dhals*), vegetables and fruit enter into all the national dietaries of India; but it is only amongst the better classes that a sufficiency of these is eaten. Accompanying this gradual fall in the nutritive values of the national diets there is a gradual decline in stature, body-weight, stamina and efficiency of the people. McCay was the first to draw pointed attention to this association, which my own observations have confirmed. In his book—*The Protein Element in Nutrition* (1912)[1]—he emphasizes the 'all-important influence exerted by food, and particularly protein, in determining the degree of muscular development, the general physical endowment, the powers of endurance and of resistance to disease, and, most important of all, the place a tribe or race has won for itself in manliness, courage and soldierly instincts'. Indeed, nothing could be more striking than the contrast between the manly, stalwart and resolute races of the north—the Pathans, Baluchis, Sikhs, Punjabis, Rajputs and Maharattas—and the poorly developed, toneless and supine people of the east and south: Bengalis, Madrassis, Kanarese and Travancorians. McCay's work was done before the days of vitamins; and while he rightly emphasized the important part played by the protein element of food in bringing about this result, we now know that other factors—vitamins and mineral elements—are concerned in it also. Inherited factors, climate, customs, caste, religion and endemic diseases no doubt contribute their share to the production of this result; but food is the paramount factor concerned. This is shown to be so by an experiment carried out some years ago (1926)[2] in this laboratory. Groups of young rats—twenty in each—were fed on certain national diets of India; care being taken to simulate in every detail the culinary practices of the races concerned. The animals were obtained from the same stock, an unusually healthy one. The experiment was so conducted that factors such as climate, atmospheric temperature, rainfall, age, body-weight, sex-distribution, caging, housing, and hygiene were the same in all groups. It was found that the nutritive values of these diets—as determined by the average body-weight of each group at the conclusion of the experiment—ranged themselves in the following order:

Diet	*Average Body-weight of Group (gm.)*
Sikh	235
Pathan	230

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[1] McCay, D., *The Protein Element in Nutrition*. E. Arnold (London, 1912).
[2] Number 118 in Bibliography.

Maharatta	225
Kanarese	185
Bengali	180
Madrassi	155

The 'Sikh diet'—the most nutritious of those examined—was made up of freshly ground whole wheat made into cakes of unleavened bread (*chapattis*), milk, and the products of milk—butter, *ghee*, curds, buttermilk—*dhal* (legume), vegetables (fresh carrots and cabbage), tomatoes, root vegetables, fresh meat with bone and fat once a week, and water. The 'Madrassi diet'—the least nutritious of those examined—was made up of washed polished rice, *dhal* (legume), fresh vegetables, condiments, vegetable oil, coffee with sugar and a little milk, a little buttermilk, *ghee* (sparingly), coconut, betel-nut and water. The respects in which these two diets differ are obvious.

Further evidence of the health-giving properties of the Sikh diet is afforded by the following experience: my stock rats are fed on this diet. The average daily strength of this stock is round about 1,000: sometimes more, sometimes less. The animals live under conditions of perfect hygiene and are exposed daily to the sun's rays. During the past three years there has been no case of illness amongst them, no death from natural causes (the older animals are killed off when no longer of use for breeding purposes), and no infantile mortality other than an occasional accidental death. Large numbers of them (1,189) at all ages up to two years have been killed and subjected to post-mortem examination without revealing any macroscopical evidence of disease except an occasional cyst (tapeworm) in the liver. Disease has been almost completely excluded by attention to three things: cleanliness, comfort, and food.

These experiences illustrate the great importance of food in relation to the physical efficiency and well-being of animals and man; the importance, also, of a proper balance of the national diets of India with respect to animal protein, animal fat, vitamins and mineral elements; and the great value, as a health-promoting agency, of the lacto-vegetarian diet used by the people of the north of India, amongst whom are some of the finest physical specimens of mankind.

Our first problem of nutrition in India—'What diet is most likely to maintain physical efficiency and health?'—has thus been solved. It is a diet composed of any whole cereal grain or mixture of cereal grains, milk, the products of milk—butter, curds and buttermilk—legumes, green leafy vegetables, root vegetables, fruit and water, with meat occasionally. I notice that the 'Oslo Breakfast',[1] which is reputed to be having such remarkably beneficial effects in Norwegian children, is of this order. To the tribes of our Indian frontier this is 'an old accustomed feast'.

One further fact in regard to the national diets of India is here deserving of note—it introduces another element into the complexities surrounding problems of nutrition in this country—that of high atmospheric temperature and drought. It was observed in this laboratory, about ten years ago, that the milk of cows subsisting on the parched pasture available during the hot months of the year contained less vitamin A than that of cows feeding on the green pasture that springs up after the rains. Generally speaking, it is safe to say that the vitamin-A content of the milk of the ill-fed and often semi-starved Indian cow is relatively low; a circumstance which is not without its effect on the well-being of the people into whose dietaries milk and milk products enter.

It is not to be supposed that the national diets of India are invariably used in their completest form by every member of the races concerned. It is only those in better class circumstances who can afford to do so. The poorer classes, according to the degree of their poverty, drop out, in part or in whole, the more expensive or less easily obtainable items: meat, milk, milk products, animal fats, legumes, fruit and vegetables. So that as the people are poorer and poorer their diets are more and more cereal in character, more and more imbalanced, more and more depleted of animal protein, animal fats, vitamins and essential mineral elements. Lower down the social scale a stage may be reached when the diet consists mainly of cereals, and lower still it may not provide even enough of these; under-nutrition is then added to faulty nutrition—a state in which millions of the Indian people exist for the greater part of every year of their lives. 'Throughout his daily work, the powerful influence of this condition of chronic semi-starvation, not merely in the poor (Indian) himself but throughout his whole race and generation, is constantly obtruding itself upon the physician, who says: "This man's constitutional malady is malnutrition, anaemia, asthenia, complicated with fever, dysentery or what not." Consequently, the first indication for treatment is a proper and nourishing diet' (Norman Chevers, 1886).[2]

Our next problem of nutrition in India has, therefore, been this: 'What are the effects, on the people using them, of diets composed mainly of cereals?' This problem may be approached in two ways, and for its proper solution it should be approached in both ways: by an epidemiological survey of diseases with special reference to dietary conditions (an undertaking so great as to be outside the resources of this laboratory), and by animal experimentation. The latter is the way I have followed.

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[1] A breakfast served free to schoolchildren and consisting of half a litre of milk, wholemeal bread with butter, wholemeal rusks, a raw carrot, an apple or orange, and whey cheese.

[2] Chevers, N., *Commentary on the Disease of India* (J. and A. Churchill, 1886).

In India we have to deal with combinations of food faults rather than with single food faults. There is, for instance, no diet in common use in India which, while lacking in any single element or complex necessary for normal nutrition, is not at the same time faulty in other regards. It may, indeed, be doubted whether any deficiency is ever complete; deficiency of vitamin C is the most likely one to be complete. It is with 'insufficiency' rather than with complete want of certain food factors that we have to deal; and with a combination of such insufficiencies. Associated with them there is, as a rule, an imbalance of the diet with respect to proximate principles; such imbalance usually takes the form of excessive richness of the food in carbohydrate. It is true that one insufficiency or another may be dominant; as, for example, insufficiency of vitamin B in rice-eaters. But upon the effects of the dominant insufficiency there are often superimposed those of other associated insufficiencies, of imbalance of the food in other regards, or of actual under-nutrition. Our problem in India is not so much one of the effects of this or that deficiency as of the effects of this or that faulty diet. What, then, are the effects on the animal organism of a diet composed wholly or almost wholly of rice? What are those of a diet composed wholly or almost wholly of wheat? And to what extent do these effects, as observed in animals, enable us to account for ill-health in man?

To begin with rice. This cereal has many deficiencies, prominent among them being that of vitamin B. In India rice is the poorest of all cereals in this complex. The effects of rice on the animal organism, either alone or in combination with other food materials in common use by rice-eaters, were studied in pigeons and monkeys. It was found that the more highly the rice was polished and the more it was washed the more rapid was the onset of symptoms; and these symptoms were usually of the same kind: polyneuritic. But no man lives on rice alone. No matter how great his poverty may be he makes some addition to his rice—a little *dhal* (legume), a little vegetable, or a little of both. These additions raise the nutritive and vitamin-B value of the diet to some extent; and it is when animals are kept on a diet of this kind—a diet in which vitamin B is not wholly lacking though insufficient for normal metabolism—that we begin to see signs and symptoms of ill-health which are of the greatest importance in relation to the origin of maladies prevailing amongst rice-eaters. These signs and symptoms are poor appetite, loss of appetite or (in monkeys) depraved appetite, failure to increase in body-weight or actual loss of body-weight, vomiting (in monkeys), diarrhoea, dysentery (specific and non-specific), colitis, slowing of the respiratory rate, lowering of body-temperature, cardiovascular depression, progressive asthenia, anaemia, disorders of the skin, oedema, nervous irritability, symptoms referable to malnutrition of the nervous systems, and intercurrent infections. The last may lend wide variety to the symptomatology; and it is here that chance comes into play in determining the kind of infection from which the animals suffer. Thus, one batch of pigeons, imported for experimental use into this laboratory, had amongst them some carriers of the invisible virus of *Epithelioma contagiosum*. The birds fed on the rice diets suffered much from this condition, while well-fed controls did not. Another batch happened to have amongst them carriers of *B. suipestifer*; the birds fed on the rice diets suffered much from this infection—itself capable of causing neuritis—the well-fed controls did not. A batch of monkeys happened to have amongst them carriers of *Entamoeba histolytica*; dysentery appeared amongst the ill-fed animals, while the well-fed—amongst whom were also carriers—remained free from it. Thus did faulty nutrition favour infection by invisible virus, bacillus, and amoeba.

It was found also that a number of other factors—age, sex, warmth, cold, damp, chill, balance of the food, previous food conditions, and, above all, individual idiosyncrasy—influenced the onset of symptoms either in the direction of precipitating or of retarding them. Those that precipitated symptoms were such as placed additional burdens on the metabolic resources of the body; those that retarded them were such as conserved these resources. Thus the addition of an excess of fats to the rice diet hastened the death of both birds and monkeys, while exposure to cold and damp precipitated the onset of oedema—an observation of significance in regard to malnutritional oedema and beri-beri.

Associated with these symptoms of ill-health profound changes were found throughout the organs and tissues of the body; these were observable even by the naked eye and the relatively crude method of histological examination. Of these changes the most conspicuous were those in the gastro-intestinal tract, the circulatory system, the endocrine organs and the nervous system. They are nowadays so well known that little further reference need be made to them; by analytical methods of experimentation many of them have since been traced to particular deficiencies in the diet.

In these observations a parallel is to be found in the poor stamina, muscular development and general physical endowment of rice-eating races, and in the low powers of endurance and of resistance to infection of the poorer classes amongst rice-eaters. A parallel also is presented in the frequent occurrence amongst them of respiratory diseases, gastro-intestinal diseases (diarrhoea, dysentery, cholera, colitis), malnutritional oedema, anaemia, skin diseases, and beri-beri. Interest in the last-named has, because of its occurrence amongst rice-eaters, overshadowed the vastly more important and more general effects of the rice-eater's diet. For, considering the millions whose staple article of diet is rice, beri-beri is a relatively uncommon disease in India. Its distribution is very limited; it is confined, as an endemic, to certain coastal areas of the north-east of Madras and Bengal. In Madras it is rarely found at a distance of more than fifty miles inland. It is practically unknown on the west coast of Madras and Bombay where as much rice *per capita* is eaten as in localities where it is endemic. Occasional small outbreaks (epidemics) occur in other parts of India, but, for the most part, these are in persons who have emigrated from endemic areas. In India endemic beri-beri is very definitely a 'place disease'. I do not here speak of 'epidemic dropsy' which some, in India, consider to be a form of beri-beri. Much of the confusion in regard to the causation of beri-beri has arisen from the fact that parboiled rice and rice which is not highly milled and polished are supposed to contain 'plenty of vitamin B'. They do not. In this laboratory true beri-beri has been produced in pigeons fed exclusively on diets of undermilled or home-pounded rice or of washed parboiled rice. A second source of confusion has been the assumption that *polyneuritis columbarum* is the same condition as true beri-beri. It is an analogous condition certainly, but not the same condition; though it may arise under precisely the same dietary conditions as true beri-beri does. Thus, if pigeons be fed on a diet simulating that in use by human beri-berics—washed, polished rice, plus 0·8 gm. of *dhal* per bird daily, the latter administered artificially—some will develop no signs either of polyneuritis or of beri-beri, though they may suffer from other maladies, within a period of 100 days; others will develop *polyneuritis columbarum*; others *beri-beri columbarum*; others again, a condition intermediate between these two states. The individual idiosyncrasy of the bird is the final factor determining which condition it will suffer from or whether it will suffer from either. These two conditions differ from each other as follows: the former is a state of polyneuritis and cardiac atrophy with or without oedema; it is most readily and most regularly produced when the rice diet is very deficient in vitamin B. The latter is a state of polyneuritis, cardiac hypertrophy and degeneration with (usually) or without (rarely) oedema; it arises when the diet contains an insufficiency of, but is not wholly lacking in, vitamin B. It is to this latter condition that the term 'true beri-beri' can alone be accurately applied. Statistical examination of my experimental data has shown that it is due to an unknown positive factor acting in association with insufficiency of vitamin B. This positive factor is produced in the bodies of the birds themselves, and is either a metabolic or a microbic poison. True beri-beri is an intoxication. It is still thought by some that the beri-beri poison can be produced in deteriorated rice outside the body. No evidence in support of this view has so far been forthcoming in the course of work in this laboratory.

There are, thus, a number of polyneuritic states which can arise in pigeons fed on rice diets: infective polyneuritis, due to a microbe such as the *B. suipestifer*; nutritional polyneuritis, due solely to avitaminosis; true beri-beri, due to avitaminosis plus an unknown positive agent arising in the bodies of the birds in consequence of the avitaminosis; and intermediate states between nutritional polyneuritis on the one hand and true beri-beri on the other. If there be this diversity of 'beri-beri-like' maladies in birds fed on rice diets, it is reasonable to suppose that a similar diversity of these maladies will be found in human beings who subsist mainly on rice. All these forms of neuritis are preventable in birds by the same means: the addition to the rice—whether it be from a deteriorated stock in use by human beri-berics or not—of a sufficiency of food materials (wheat, tomatoes, legumes, etc.) rich in vitamin B. Human beri-beri, as it occurs in India, is also preventable by the same means and has been so prevented in jails where it was endemic for years. The prescription of ancient Indian hakims—'stop eating rice and take a diet of whole wheat and milk'—can hardly be bettered.

So much then for the rice-eater's diet. What of the wheat-eater's? If animals (rats) be fed on an exclusive diet of whole wheat the mortality amongst them is very high. Pulmonary infection is the chief cause of death. If to the diet of whole wheat some good olive or sesame oil—which are poor, but not wholly lacking, in vitamin A—be added, together with a salt mixture to make up for certain mineral defects in the wheat, the animals live longer and afford greater opportunity for the study of the effects of a diet comparable in composition to that used by the poorer class wheat-eater. The main deficiency of this diet is now one of fat-soluble vitamins. Its effects are exhibited as metaplasia of epithelia throughout the body—a change now recognized as characteristic of vitamin-A insufficiency. Infections of the eye, the nasal sinuses, the lungs, the intestinal tract and the urinary tract are common; urinary calculus is frequent; and goitre is occasionally met with.

In the course of experimental work in this laboratory many variations of deficient diets, having one or other cereal grain or cereal product or mixture of such as their basis, have been used with results which manifest themselves, for the most part, as 'itis's' of various kinds and location. These need not be enumerated but some reference may be made to three conditions—'stone', 'goitre', and 'peptic ulcer', which in India are problems of moment.

The distribution of 'stone' is peculiar; it occurs, for the most part, in the north of India and is relatively rare in the south. It is a disease of wheat-eaters rather than of rice-eaters. Experimental work in this laboratory has shown that the cereal grains in common use in India vary in their stone-producing potency, wheat having the highest, rice the lowest potency in this regard, while the other cereals occupy an intermediate position between these two extremes. The distribution of 'stone' is, therefore, related to the distribution of cereal crops. The stone-producing potency of white flour is relatively low; and as white flour contains no more vitamin A than whole-wheat flour, it is obvious that in the process of milling some substance favourable to stone production is removed from the whole grain. There are two classes of factors (apart from infection and foreign bodies in the urinary tract) concerned in the causation of stone: negative ones—vitamin-A deficiency and phosphate deficiency; and positive ones—an unknown substance existing in different amounts in different cereals, and excess of lime in the diet. Cattle stones are, in India, almost invariably composed of calcium carbonate. The dietary conditions under which they arise in nature or are produced under experimental conditions in the laboratory are the same: deficiency of vitamin A and deficiency of phosphates relative to the amount of lime in the diet. Work in this laboratory has convinced us that, in India, urinary calculus is usually a disease of faulty nutrition.

The distribution of 'goitre' is also peculiar: it occurs chiefly in Himalayan regions. In these the iodine content of the soil is low and no doubt also that of the food materials grown upon it. But the iodine content of the urine is not significantly higher in non-goitrous than in goitrous persons in these regions; and while admitting that iodine deficiency may favour the development of certain kinds of goitre, such deficiency is not regarded as the essential cause of the disease. With the possible exception of the adrenal glands and thymus, no organ or tissue of the body is more sensitive to food conditions than the thyroid. The iodine content, the fat content, the lime content, the phosphate content, the vitamin content of the food—all these influence its size; as do certain unknown substances in food materials such as cabbage and ground-nuts. Its size also is influenced in certain circumstances by insanitary conditions of life. Iodine is by no means the be-all and the end-all of goitre. Four aetiologically distinct types of goitre have been produced in this laboratory—the hyperplastic, the hypertrophic, the colloid and the lymphadenoid—but all have this in common: they are preventable by the same means. This means is the provision of a perfectly balanced diet such as the lacto-vegetarian one previously described. Thus, insanitary condition—a positive goitrogenic agency—will not cause goitre when the animals are properly fed; it will cause goitre when they are not. Goitre is, in the main, a disease of faulty nutrition; but, like beri-beri and like urinary calculus, both negative and positive factors are concerned in its causation.[1]

'Peptic ulcer' has also a peculiar distribution. It is very common in the south of India—particularly in Travancore. It has been shown in this laboratory that the tapioca diet of the poorer class Travancorian will cause this condition in 27 per cent of albino rats fed upon it; that of the poorer class Madrassi in 11 per cent; while the lacto-vegetarian diet of the Sikhs affords the animals complete protection against it. Some ten years ago it was observed, in this laboratory, that deficiency of vitamin C was capable of causing duodenal ulcer in guinea-pigs.

A pernicious type of anaemia may occur in albino rats when they are fed on a diet of oatmeal, linseed meal and patent flour. It is due to the rat-louse-borne organism: *Bartonella muris*. As is well known, this organism gives rise in these animals to a profound anaemia on removal of the spleen. It is of significance, in regard to such maladies as malaria, typhus, relapsing fever, and Kala-azar—all widely prevalent in India and favoured in their course and development by famine conditions—that the protective resources of the spleen can be injured by faulty nutrition in a way comparable to that brought about by splenectomy.

Other diseases of faulty nutrition—keratomalacia, night-blindness, rickets, osteomalacia, tetany, dental caries, scurvy, pellagra, anaemia of pregnancy, lathyrism—all concern us, to a greater or lesser extent in India; and many other conditions, such, for instance, as cataract and sprue, may have a malnutritional basis of the nature of which we as yet know but little. Keratomalacia is common, and is the chief cause of preventable blindness (Wright, 1931).[2] It occurs in undernourished, poverty-stricken persons whose diets are not only deficient in vitamin A but in other vitamins as well. 'In all probability it requires an initial multiple vitamin deficiency, with a secondary multiple dysfunction of glandular structures to account for the whole picture of degeneration, loss of function, wasting, necrosis, secondary infection and death which we see in keratomalacia' (Wright, 1931).[2] Night-blindness is also common—well known to ancient Indian hakims who treated it by the administration of liver. It is frequently associated with lathyrism in localities where the latter condition prevails (McCombie-Young, 1927).[1] 'In northern India and Kashmir rickets in its various forms, osteomalacia, late rickets and infantile rickets, tends to occur in any race or caste wherever there is extreme deficiency of sunlight or diet, or more frequently where there is a relative deficiency in both these factors' (Wilson, 1930–31)[2]. It is of greater severity amongst those who observe purdah conditions of life. Osteomalacia accounts for much maternal mortality in childbirth (Vaughan).[3] Tetany is frequently associated with rickets; it is endemic in certain valleys of the Himalayas. Dental caries and hypoplasia are widespread amongst Indians whose diets are composed mainly of cereals and are deficient in fat-soluble vitamins and vitamin C. If deficiency of vitamin D be the chief cause of dental caries it is obvious that tropical sunlight does not provide enough for its prevention. Scurvy, usually in minor form, is widespread throughout the whole of India; and pyorrhoea alveolaris is frequently to be found in persons whose diets contain far too little fresh vegetable foods. Pellagra appears to be relatively rare. The anaemias of pregnancy are common; they are malnutritional in nature, occurring in women whose diets are both quantitatively and qualitatively deficient (Wills, 1928–31). [4,5] Epidemiological investigations, carried out by McCombie-Young (1927)[1] from this laboratory, have shown that lathyrism is associated not only with the predominance of *Lathyrus sativus* in the diet but with under-nutrition and deficiency of fat-soluble A.

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[1] Number 8 in List of Books and Memoirs.

[2] Wright, R. E., *Lancet*, i, 800, 1931.

The problem in connection with all these diseases is no longer one of lack of knowledge of their nature, nor of their means of prevention; but one of the improvement of conditions of living and of food supply of the people. Indeed, the greatest of all problems in India at the present time is the adjustment of the population to its food supply. It is one that is capable of solution only by the people themselves: by the exercise of self-help; by the jettisoning of old habits and customs unsuited to modern economic conditions; by improvement in methods of agriculture, animal husbandry and industry; and, above all, by restraint in reproduction.

Recently (1931),[6] I had occasion to contrast the incidence of disease in 2,243 improperly-fed albino rats with that in the well-fed stock rats in this laboratory. It was shown that while the former exhibited a large proportion of the maladies included in the calendar of human ailments, the latter were remarkably free from disease of any kind. The only significant difference in their conditions of life was the improper feeding of the one 'universe' and the proper feeding of the other. It seems to me that, however deeply we may delve into the minutiae of the relationship of faulty nutrition to disease, the essence of the whole matter will be found to lie in this: the use of a properly constituted diet is a sure means to the attainment of physical efficiency and health. Such a diet is the lacto-vegetarian one in use by certain vigorous and resolute races of northern India.

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[1] McCombie-Young, T. C., *Indian J. med. Res.* 15, 453, 1927.

[2] Wilson, D. C., *Indian J. med. Res.* 18, 975, 1930–1.

[3] Vaughan, K. O., *The Purdah System and its Effect on Motherhood* (W. Heffer and Son, Cambridge, 1928).

[4] Wills, L., *Brit. med. J.*, i, 1059, 1931.

[5] Wills, L., and Mehta, M. M., *Indian J. med. Res.*, 17, 777, 1929-30.

[6] Number 139 in Bibliography.

A Good Diet and a Bad One: An Experimental Contrast[1]

I. INTRODUCTION

In the concluding paragraph of a paper dealing with the nutritive value of wheat and *paddy*,[2] published in this number of the *Indian Journal of Medical Research* (p. 638), it is pointed out that those Indian races, like the Sikhs, whose diet consists of whole wheat (*chapatties*), milk, milk products, green leafy vegetables and fruit, with meat occasionally, provide examples of the highest type of physical efficiency met with in this country, or indeed, in any part of the world. The conclusion is drawn that this is due, in the main, to the high nutritive quality of whole wheat, as compared with other staple food grains, such as rice, and to the manner in which wheat is combined by wheat-eating races with other 'protective' and vitamin-A-containing foods. This conclusion was subjected to the test of experiment; and the effects, on omnivorous animals, of a 'good diet', constituted as above, were compared with those of a 'bad one', such as is used by many Western people. The results of this comparison are recorded in the present paper.

II. THE EXPERIMENT

Two colonies of half-grown rats were employed; each comprising 20 animals of which 12 were males and 8 were females. They were selected from among ten or twelve litters of approximately the same age, and were so distributed between the two colonies as to ensure, as far as possible, that the growth potential of the two groups would be alike. The aggregate weight of the animals in each colony was the same—2,540 gm. They were housed in the same room, caged in large hygienic cages in a precisely similar way, and were equally well tended.

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[1] Extract from number 118 in Bibliography.

[2] Number 117 in Bibliography.

One colony received 'a good diet', designed to resemble that eaten by the Sikhs. It consisted of *chapatties*, made of whole-wheat flour; uncooked, green vegetables; fresh fruit (tomatoes, etc.); sprouted *gram* (legumes); butter; fresh whole milk; and fresh meat occasionally. A liberal allowance of butter was given spread over the *chapatties*; milk was supplied in amounts of approximately 300 c.c. daily; fresh meat was given every week to the amount of 2 oz. for the whole colony. Liberal quantities of *chapatties*, sprouted *gram*, uncooked vegetables and tomato—to take the place of fruit—were given, so that the animals could select for themselves the amounts of each they cared to eat. Any food not eaten during the day was discarded when the cages were cleaned each morning.

The second colony received a diet which was ultimately shown to have been 'a bad one'. It was designed to resemble that eaten by many Western people of the poorer classes. It consisted of white bread, made from American white flour and obtained from the local bakery; vegetables—cabbage, carrot, potato, etc.—cooked in water to which pinches of bicarbonate of soda and common salt were added; a substitute for margarine, consisting of coconut oil to which 100 grains of boric acid were added to every pound of the oil; tinned meat, which had been exposed to formaldehyde vapour for several hours; tinned jam; tea, well sweetened with sugar, to which was added enough milk to give it the customary tinge; and water. The animals acquired an extraordinary liking for the tea; consuming as much as 600 c.c. daily, and therewith approximately 20 gm. of sugar and 20 c.c. of milk. The boracized coconut oil was lightly smeared on slices of the white bread and the whole covered with a liberal coating of jam. The amount of this boracized substitute for 'margarine' eaten by each rat was approximately 1·5 gm. daily. The potted meat was given in like amount to the fresh meat in the first colony: 2 oz. weekly. Of the other ingredients of the food—the tea, the bread and jam and the cooked vegetables—the animals were allowed to eat and drink as much as they liked. This diet had added to it two of the commoner food preservatives, so widely used in Western countries:[1] boric acid and formaldehyde. The former is commonly present, sometimes in large amounts, in butter, margarine, cream, imported liquid eggs, sausages, potted meat, potted fish, and some beverages; while it is also used for packing bacon and hams.[1] As much as 175, 140 and 110 grains per pound of boric acid have been found in margarine, butter and bacon respectively. The amount in the first two is usually about 0·5 per cent, or 35 grains per pound.[1] I added 100 grains to the pound of coconut oil in order that other sources of boric acid—bacon, liquid eggs, sausages, etc.—not included in the above diet, but commonly included in the dietaries of Western people, might be covered; and in order that the amount of boric acid ingested by the rats might be approximately proportionate to that ingested by these people. The potted meat given to the animals was exposed to formaldehyde vapour in order to simulate the Langley process of treating chilled meat for import. In all probability the tinned jam contained sulphurous acid as a preservative;[1] so that in addition to the faults in composition and in quality of this diet (insufficiency of vitamins and of certain mineral salts and excessive richness in carbohydrates) there were present in it several food preservatives the effects of which on the animal organism may not have been negligible.

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[1] *Final Report of the Departmental Committee on the Use of Preservatives and Colouring Matters in Food* (H.M. Stationery Office, London, 1924).

The experiment commenced on the 21st January 1926, and was continued for six months. During its course the animals were kept scrupulously clean; and were comfortably bedded in fresh straw. They were given sunbaths of two-hours' duration—while in their cages—twice a week.

III. RESULTS OF THE EXPERIMENT

1. *Mortality*

On the termination of the experiment there were 17 animals alive and well in the colony which received the 'good diet': 10 males and 7 females. In the colony which received the 'bad diet' 11 animals were alive at the end of the experiment: 5 males and 6 females. The mortality from all causes in the former colony was thus 15 per cent; in the latter 45 per cent. But whereas the survivors in the first colony were well grown, sleek-coated, strong and active, those in the second colony were ill grown, poor-coated, weakly and listless.

2. *Causes of Death*

Of the three animals which succumbed in the well-fed colony one died from injury to the abdomen. At post-mortem examination it was found to be excellently nourished; its organs being in perfect health. It was a female and pregnant; there were six foetuses in the uterus. A second animal died of pneumonia; the gastro-intestinal tract was not diseased. The third died from causes which I was unable to discover at post-mortem examination; a small cyst containing an embryo tape-worm was present in the liver but no other abnormality could be found.

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[1] Ibid.

Of the nine animals which died in the ill-fed colony three were killed and eaten by their fellows; so completely eaten in each case that little or nothing remained for post-mortem examination. (At one time during the course of the experiment I feared that cannibalism—that sure sign in rats of a faulty diet—might put an end to the experiment. Resort had, therefore, to be made to separating each animal in this group from its fellows every night. This was done by putting each rat into a straw-lined and perforated biscuit tin; the animals being restored to the colony cages each morning. Later a small quantity of fresh vegetable food was given two or three times a week, in addition to the diet above-mentioned, when cannibalism ceased.) The immediate cause of death in the other six animals was broncho-pneumonia; and this at a time when broncho-pneumonia was so rare in my stock animals that only three cases of the disease occurred during the six months in a rat population which averaged at that time 375 daily. One consequence, therefore, of the 'bad diet' was to lower the resistance of the lungs to attacks by microbic agents of disease: a consequence of faulty food, deficient in vitamins, which has already been emphasized by Cramer.[1]

3. *Other Post-mortem Findings*

Of these the most constant and the most important were changes in the gastro-intestinal tract which impaired its functional capacity. In illustration of this point I append the notes of two cases dictated at the time the post-mortem examinations were made: 'On opening the abdomen the first thing observed is the extreme dilatation and thinning of the whole gastro-intestinal tract; atony of the bowels; ballooning and transparency; intestinal stasis; giving the appearances now so familiar to us in deficiently-fed animals, and first observed in pigeons and monkeys in 1919.'[2] Again in another case: 'The case presents an extraordinary contrast to all other rats' intestines seen up to date. The lumen of the bowel is very much narrowed; the bowel being in its whole course hardly thicker than a piece of grocer's string. There is no distension of the bowel nor "air-locks". Intestinal stasis is marked; the lower part of the bowel is filled with hard, oval, faecal masses situated one above the other which, with the attenuated bowel between them, resemble a string of beads strung at bead-distance intervals. The stomach is very small and is not dilated; it is filled with coffee-ground-like material; some of which washes off in water but much of which is adherent to the congested mucous membrane and can be removed only by scraping. About the middle of the proximal portion of the stomach there are three mammiform areas each having a small crater-like depression at the top.' These areas which may be either viliform or mammiform, were found in this situation in three out of the six animals, in which post-mortem examination was made, but never, so far, in well-fed controls. On histological examination they were seen to be papillomatous outgrowths of the stratified epithelium lining the proximal part of the stomach. These notes will serve to indicate that the diet on which this colony was fed was such as favoured the production of an unhealthy and inefficient state of the gastro-intestinal tract, and an abnormal growth of epithelium in the proximal portion of the rat's stomach.

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[1] Cramer, W., *Proc. roy. Soc. Med.*, 19, 6, 1925.

[2] Number 73 in Bibliography.

4. *Fertility*

Although the conditions of colony life are not the most favourable for reproduction, yet 20 litters were born in the well-fed colony during the six months the experiment lasted. In these 20 litters there were 134 young, all of which were reared to maturity. Each litter was removed, with the mother, shortly after birth to a separate cage; the mother meanwhile continued to be fed on the same diet. After the young were weaned the mother was returned to the colony cages. There was no tendency to the eating of new-born rats by the animals in this colony. In the ill-fed colony two litters were born during the first few weeks of the experiment. One litter consisted of seven, the other of four. Of the eleven young two died, and the remaining nine were eaten before the attendants removed them from the colony cage. The 'bad diet' was not, therefore, as conducive to fertility as the 'good diet'.

5. *Body-weight*

The difference in body-weight of the two colonies is sufficiently indicated by the photographs (see the original publication). Starting from the same point at 2,540 gm., the two curves diverged. The aggregate weight of the well-fed colony rose steadily; that of the ill-fed colony fell steadily. At the points at which deaths occurred in either colony an arrow indicates the event. The fall in the aggregate weight curve of the ill-fed colony was of course due mainly to losses by death; but the chart illustrates in a striking way the extent to which the ill-fed colony suffered.

IV. CONCLUSION

This experiment demonstrates that a diet composed of whole wheat, milk, milk products, sprouted legumes, uncooked vegetables and fruit with fresh meat occasionally, far surpasses in nutritive value that composed of white bread, tea, sugar, margarine, jam, boiled vegetables and tinned meat, to which the common food preservatives—boric acid, formaldehyde vapour and sulphurous acid—are added. Not only does the former promote physical efficiency and health but the latter gives rise to stunting of growth, to physical inefficiency, and oftentimes to disease. The maladies of which the bad diet is so apt to lay the foundation are lung disease and gastro-intestinal disease. I have repeatedly drawn attention to the influence of faulty and ill-balanced food in causing the gastro-intestinal diseases which are so common at the present day.[1] The results of this experiment furnish additional proof of this influence and suggest that the commoner food preservatives may contribute their share to the harmful effects of such a food. The high incidence of lung disease in the ill-fed group emphasizes no less strikingly the influence of what one may call the 'white-bread-margarine-and-tea-diet' in favouring the operation of pathogenic agents which attack the lungs.

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[1] Number 3 in List of Books and Memoirs.

CHAPTER VII

Lectures and Addresses

Some Surgical Aspects of Faulty Nutrition[1]

I. INTRODUCTION

The laboratories of the Indian Research Fund Association, devoted to the study of diseases associated with faulty nutrition, are located at Coonoor in the Blue Mountains (Nilgiris) of southern India, 6,000 feet above sea-level. Their location is fortunate, for the temperature is equable, never very hot or very cold: the mean winter temperature rarely falls below 50° F., the mean summer temperature rarely reaches 80° F. A good deal of rain falls in these hills, Coonoor coming within the range of both the south-western and the north-eastern monsoon: the former brings with it only occasional heavy showers, while the latter may involve us in heavy rainfall during November, December, and January. But it is rare that a day passes without some hours of bright sunshine and clear skies. Conditions are such that no elaborate buildings are required for the animals. Indeed, I have been content with corrugated-iron sheds, roofed with the red tiles of the country, and having floors tiled, sloped, and adequately drained. I am fortunate also in having a large staff of animal attendants, who are now highly skilled in their work. In these favourable circumstances, it is possible to ensure ideal conditions of hygiene and exposure of the animals to sunshine practically every day the whole year round. A simple but adequate means of sterilizing the animal cages is adopted, and the hosepipe and creosote solution are used freely on the tiled floors. The walls are whitewashed frequently. The test of cleanliness is a simple but severe one. In an animal room of some $30' \times 15'$ there may be as many as 500 rats. Should the visitor be made aware of their presence by his sense of smell then there is something wrong with the sanitation. I may add that he rarely is.

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[1] Extract from number 139 in Bibliography.

II. FREEDOM OF WELL-FED ANIMALS FROM DISEASE

In these conditions there live some 1,000 stock albino rats—the source from which the large numbers of young animals required for my work are obtained. For this work I use on the average 1,100 animals a year. The pairs are kept in roomy, netted-wire cages, screened and straw-filled, in which they find the peace and comfort necessary for fruitful breeding. As a rule, five or six litters are taken from each pair, and the older animals are thinned out at the age of 2 years—a lifespan said to correspond approximately to the first forty to fifty years of life in man. The average number in each litter is eight, but litters of twelve are frequent, and those of fifteen are not uncommon. The mothers invariably rear the whole of their young.

This stock is fed on a diet similar to that eaten by certain peoples of northern India, among whom some of the finest physical specimens of mankind are to be found. The diet consists of whole-wheat flour, unleavened bread (*chapattis*) lightly smeared with fresh butter, sprouted Bengal *gram* (legume), fresh raw carrots and cabbage *ad libitum*, unboiled whole milk, a small ration of raw meat with bones once a week, an abundance of water, both for drinking and for washing purposes.

The point of these somewhat lengthy, but necessary, details is this: during the past two and a quarter years there has been no case of illness in this 'universe' of albino rats, no deaths from natural causes in the adult stock, and, but for a few accidental deaths, no infantile mortality. During this period I have myself performed complete post-mortem examinations on 1,189 of these rats, ranging in age from the newborn to 2 years. In none have I encountered any macroscopical evidence of disease, with the exception of an occasional cyst in the liver, containing tape-worm larvae. How the animals became infected with tape-worm I do not know, unless it be from the straw bedding which they nibble. Both clinically and at post-mortem examination this stock has been shown to be remarkably free from disease. It may be that some of them have cryptic disease of one kind or another, but, if so, I have failed to find either clinical or macroscopical evidence of it. Disease and death have been excluded, almost completely, by minute attention to three environmental conditions: cleanliness, comfort. and food.

III. HIGH INCIDENCE OF DISEASE IN ILL-FED ANIMALS

I wish now to turn to my experimentation rooms. Here are the same corrugated-iron huts, the same cages, the same scrupulous cleanliness, if anything more scrupulous than in my stock-animal houses; for here there are attendants, armed with forceps and crum-tray, who pass from one cage to another removing faeces which may occasionally adhere to the half-inch meshes of the screens on which the animals live. There is no coprophagy; it is not allowed. Nor do we meet with the phenomenon of 'refection'. Here the animals are exposed in the same way to the sun's rays. But they live in separate cages, as do the controls for each experiment—isolated from their fellows; they are thus less contented than their more fortunate kith and kin in the stock-animal rooms, and they are more exposed to the effects of chill, since they cannot be given straw bedding, though each evening they are given bedding of clean cotton-waste. The main regard in which they differ from the stock animals is in their food, which is always faulty in some way or another. Further, as my business is to learn, as far as I can, how the foods eaten by the people of India are related to disease, synthetic diets are used comparatively rarely, and then only for special purposes. The materials entering into the various faulty dietaries are usually those in use by the people of India; sometimes actual Indian dietaries are used.

During the last two and a quarter years I have examined 2,243 of these improperly-fed rats at post-mortem examination—that is to say, during the same period in which I failed to find disease in the universe of stock rats. The following are the morbid states I have encountered:

(1) *Lung diseases:* pneumonia, broncho-pneumonia, bronchiectasis, pyothorax, pleurisy, haemothorax.

(2) *Diseases of the nose and accessory sinuses:* sinusitis.

(3) *Diseases of the ear:* otitis media or pus in the middle ear.

(4) *Diseases of the upper respiratory passages:* adenoid growths.

(5) *Diseases of the eye:* conjunctivitis, corneal ulceration, keratomalacia, panophthalmitis.

(6) *Gastro-intestinal diseases:* dilated stomach, gastric ulcer, epithelial new growths in the stomach, cancer of the stomach (in two cases only), duodenitis, enteritis, gastro-intestinal dystrophy, stasis.

(7) *Diseases of the urinary tract:* pyonephrosis, hydronephrosis, pyelitis, renal calculus, ureteral calculus, dilated ureters, vesical calculus, cystitis, incrusted cystitis.

(8) *Diseases of the reproductive system:* inflammation of the uterus. ovaritis, death of the foetus *in utero*, premature birth, uterine haemorrhage, 'hydrops tesitis'.

(9) *Diseases of the skin:* loss of hair, dermatitis, abscesses, gangrene of the tail, gangrene of the feet, subcutaneous oedema.

(10) *Diseases of the blood:* anaemia, a 'pernicious' type of anaemia. *Bartonella muris* anaemia.

(11) *Diseases of lymph and other glands:* cysts in the sub-maxillary glands and accessory glands in the base of the tongue, abscesses in the same, and occasionally also in the inguinal glands, enlarged mesenteric, bronchial, and other lymph glands.

(12) *Diseases of the endocrine system:* lymph-adenoid goitre, enlarged adrenal glands, atrophy of the thymus, and, very occasionally, haemorrhage into the pancreas.

(13) *Diseases of the nervous system:* polyneuritis.

(14) *Diseases of the heart:* cardiac atrophy, occasionally cardiac hypertrophy, myocarditis, pericarditis, and hydropericardium.

(15) *Oedema.*

Not infrequently animals are found to be suffering from more than one of these diseases.

I say nothing of diseases of the bones and teeth, since the diets were not specially designed for their production, and the practice of exposing the animals to sunlight—a practice followed because the average Indian is daily so exposed—probably compensated for any lack of vitamin D in the diets. But mention might be made of crooked spines and distorted vertebrae and of imperfect teeth, which are encountered not infrequently. The list I have given includes only those morbid states which I have myself seen (there may have been, and no doubt were, others which I failed to see); it is a list prepared from the post-mortem records of the 2,243 imperfectly-fed animals.

Here, then, is an experiment on a large scale extending over a period of two and a quarter years. On the one side there is, as controls, a community of hygienically housed rats, fed on a well-balanced diet composed of natural foodstuffs—whole wheat, pulses, raw milk, butter, fresh vegetables, and fresh meat with fat and bones occasionally, so combined as to provide in proper amount and proportion all elements and complexes necessary for normal nutrition. On the other, there is a community of rats, also hygienically housed, but fed on ill-balanced diets composed mainly of cereal grains or cereal products and vegetable fats with little or no milk, butter, and fresh vegetables. The contrast between these two communities is remarkable; and I claim for this experiment that it proves conclusively that one-sided diets which are disproportionately rich in cereals and poor in animal fats, milk, and fresh vegetables are capable of inducing in albino rats a large proportion of the diseases included in our calendar of human ailments. I may add that of all the faulty diets I have used, that composed of white bread, margarine, tea, sugar, jam, preserved meat, and scanty overcooked vegetables—a diet in common use by many people in this country—proved to be one of the worst, and most likely to be associated in rats with many of the morbid states I have mentioned, especially diseases of the lungs and of the gastro-intestinal tract.

Rats are not the only animals I use; guinea-pigs, rabbits, pigeons, and monkeys, are also employed. In them I have found many of the above-mentioned diseases, and some others besides. Of the latter I may mention the following: pre-scorbutic states, scurvy, and duodenal ulcer in guinea-pigs, hyperplastic goitre in rabbits, epithelioma contagiosum, polyneuritis, and true beri-beri in pigeons, and ulcerative colitis in monkeys. Two conditions I have not, so far, encountered: gall-stones, observed by Fujimaki (1926), de Langen (1929), and others; and cataract, observed by Eckstein and Szily (1924).

In every species—pigeons, rats, guinea-pigs, rabbits, and monkeys—I have found the same thing: properly-fed animals remain remarkably free from disease, improperly-fed animals are remarkably subject to it. It is reasonable, therefore, to assume that the human species is no exception to this rule, and that many of the ailments to which man is erroneously supposed to be heir are the outcome of his improper feeding. Some may hold that it is not possible directly to translate to human experience the results of an experiment such as that just described. This may be true, if we seek to do so too rigidly and fail to take sufficient count of other environmental factors to which human beings may be exposed. But, in general, the results of an experiment of this kind do, in my opinion, apply to man, and point the way to a solution of many aetiological problems connected with his physical infirmities.

IV. DEFICIENCY IN VITAMIN A

In the above list of diseases there are many of interest to the surgeon. Sinusitis, adenoid growths, otitis media, gastro-duodenal ulcer, gynaecological ailments, certain types of goitre, and urinary calculus are some of them. At first sight it would appear that morbid states so dissimilar as adenoids and stone in the bladder had nothing in common, yet aetiologically they are not so far apart. All these surgical conditions were found to have this in common: they occurred in animals whose ill-balanced diets contained little or no vitamin-A-bearing food materials, such as raw milk, butter, cod-liver oil, carrots, and fresh green vegetables. In my hands these food materials, when suitably combined, have protected my animals from these diseases, and I do not doubt that in the hands of the surgeon they will go far to protect his human patients from them and facilitate their cure and non-recurrence after operation. I lay stress on the food materials themselves rather than on any particular ingredient of them, or any particular quality possessed by them, believing, as I do, that in nature's laboratory all elements and complexes needed for normal nutrition are combined in a way which we cannot wholly achieve, and that the health-giving properties of food are largely dependent on this combination. For my own part, I have been able to devise no synthetic diet which can equal in these properties a mixture of natural food materials such as that on which I feed my stock rats and on which some of the finest physical specimens of mankind are reared. Nevertheless, a principal fault of the diets I have used, and one which is in considerable part responsible for the surgical diseases I have mentioned, is insufficiency of the substance or quality which we speak of nowadays as vitamin A. The effects on the organs and tissues of the body of the insufficient use of vitamin-A-bearing foods have thus a particular interest for the surgeon.

(Here followed a lantern-slide demonstration in which the lecturer showed the typical keratinization of epithelia, the concourse of lymph cells, the secondary inflammatory changes, the ulceration of, and epithelial new growths in, the stomach, and the lymph-adenoid goitre occurring in rats fed on diets containing an insufficiency of vitamin-A-bearing ingredients.)

The sites in which these changes have so far been found in experimental animals are the nares, larynx, trachea, bronchi, sub-maxillary glands, parotid gland, and the accessory salivary glands of the tongue and pharynx; the pancreatic duct, bladder, ureter, and pelvis of the kidney; the uterus and oviduct; the epididymis, prostate, and seminal vesicles; the conjunctiva, Meibomian gland ducts, cornea, lacrymal gland, Harderian gland, and the extra-orbital (lacrymal) gland; the thymus (Wolbeck and Howe, 1925). To this list I must myself add the thyroid gland. 'The distinctive or peculiar gross changes are those due to mechanical factors sequential to the formation and retention of desquamated, keratinized epithelial cells' (Wolbeck and Howe, 1925). Thus cysts, bronchiectasis, hydronephrosis, dilatation of the bladder and ureters may be produced by blockage of ducts or other passages.

These changes occur more readily, and within a shorter time, in young than in older animals—a thing to be expected in the growing animal. They are focal in distribution, and may be confined to narrow or to wide areas, to a few tissues or to many. They vary in their location in different species of animals and in different individuals of the same species. I have, for instance, found the adenoid-like growths in the upper respiratory tract in rats to all appearances normal except for subnormal growth. They are best seen and more widespread in animals fed on synthetic diets devoid of vitamin A; but since man's food is rarely or never wholly lacking in this factor it is of importance to realize that they occur also in animals fed on human dietaries which are by no means devoid of it, though containing it in insufficient quantity. It seems probable that these changes are helped in their occurrence by the existence of other food faults in the diet, such, for instance, as deficiency of suitable protein and mineral elements, and by the condition of semi-starvation into which the animals fall. It seems probable also that other environmental conditions, such as climate, altitude, humidity, may favour or hinder their occurrence. Thus it is universally agreed that the changes in the eye and its neighbourhood are, in rats, the most frequent; but they are not so in the climate of Coonoor; indeed, the eye is often not affected when other tissues are. I mention these matters to illustrate the interplay between nutrition and other environmental conditions (climatic and bacterial) in giving rise to the final morbid state. The worn tyre may travel far along the smooth-surfaced road before encountering a flint; its course along the flinty byway is less secure. So it is with the epithelial treads of the body surfaces when deteriorated by faulty nutrition.

The varying occurrence and location of the changes due to vitamin-A deficiency are among the most interesting things about them. Thus in monkeys fed on a diet said to be complete in other regards, but lacking a sufficiency of vitamin A, eye changes, sinusitis, and mastoiditis, so common in rats, are, as Tilden and Miller (1930) have lately shown, conspicuous by their rarity. Twelve years ago (1919) I demonstrated that the colon was of all organs in monkeys the most sensitive to faulty nutrition; and the recent work of Tilden and Miller, while confirming this observation, re-emphasizes the importance of vitamin-A deficiency in causing the ulcerative colitis which is so conspicuous a feature in these animals. The monkey's colon is also very sensitive to deficiency of other vitamins (McCarrison, 1919), particularly of vitamin C, 'which causes a condition varying from local congestion and thickening of the mucous membrane to one indistinguishable from ulcerating and sloughing dysentery' (Mackie and Chitre, 1928).

In some of these respects man resembles the rat more than the monkey. Thus he is very susceptible to the eye changes resulting from insufficiency of vitamin-A-bearing foodstuffs in his diet, if one may judge by the prevalence of keratomalacia in the Madras Presidency, and by its amenability to treatment by cod-liver oil (Wright). But I suspect that he resembles the monkey in the sensitiveness of his colon to food deficiency; the number of cases of ulcerative colitis of 'unknown' cause (Menon, 1930) occurring in India is sufficient to justify this suspicion. But however the changes vary, either as to extent or location, they are always to be found in animals of all species so far examined—rats, guinea-pigs, pigeons, fowls, and monkeys—and in man himself. Reference has already been made to their occurrence in the eye, and its neighbouring tissues, in Madrassis, and to its proven association with the specific deficiency. But there are few post-mortem studies of pure vitamin-A deficiency in man. Fortunately, there is one: I take it from a paper by Wolbeck and Howe (1925):

'*Vitamin-A Deficiency in the Human.* There has been but one pathological description of a fatal human case (Wilson and du Bois). This post-mortem, done in the pathological service of one of us at the Children's Hospital, is adequately recorded. We have recently re-studied the tissues and can add nothing of importance. Keratinization of the epithelium of the renal pelvis and large size of Hassall's corpuscles in the thymus were overlooked. The keratinization of the pancreatic ducts is more striking than any seen by us in the pancreas of rats. In respect to the keratinizing changes in the lungs, uterus, submaxillary gland ducts, and thymus, the picture was identical with that in our experimental rats. The order of changes in the human case was somewhat different, in that the salivary glands showed only slight changes. The peculiar swollen epithelial cells with nuclear inclusion bodies in the ducts of the parotid and submaxillary glands are unlike any changes seen in rats. The lacrymal gland showed only slight changes and no keratinization. The eyes were not removed for study.

'The importance of this human case is that it did show the epithelial changes which we have produced in rats, and, therefore, contributes irrefutable evidence for an important part of our thesis to the effect that vitamin-A deficiency affects epithelial tissues in a specific manner.'

The testimony of these experienced observers is of the highest value, and leaves no room for doubt that the tissue changes occurring in the lower animals, consequent on the insufficient supply of vitamin-A-bearing foodstuffs in the diet, occur also in man. I again emphasize the word 'insufficient', since, in my own experience, and in that of Tilden and Miller (1930), in monkeys the diets associated with them are not necessarily devoid of vitamin A, though always they are poor in this factor.

These changes are independent of infection, though infection is often superimposed upon them. Indeed, it is because of them that infection becomes possible, since they occur for the most part in 'outside' coverings of the body; the respiratory passages, the urinary tract, the reproductive tract, the conjunctiva, the nasal passages, the ear, and the ducts of organs. They are breaches in the walls of the body's defences, through which the invading microbe may enter. In this sense vitamin A is 'anti-infective'; but the 'anti-infective' quality is shared with other vitamins—C, B, and D—though exhibited by them in other ways.

Two points of interest to the surgeon remain to be mentioned: (1) If rats, fed on a diet deficient in vitamin A, be artificially infected with a bacterium, such as the Breslau bacillus (paratyphoid), they usually die from the resultant infection. But some may live, and in them the infection persists in the lymph glands 'for a very long time after the general infection has been overcome' (Lassen, 1930). It seems to me probable that chronic enlargement of lymph glands in childhood, due usually to infection of one kind or another, may often be due to such persistence of infection as a result of a vitamin-A-deficient diet. Further, it seems probable that the focal breakdown of the tissue defences induced by this deficiency may be concerned in the causation of those 'septic foci' about which so much is heard nowadays. (2) I have spoken above of breaches in the walls of defence against bacterial invasion consequent on the use of vitamin-A-deficient diets, and I have mentioned that other vitamins may also exercise an anti-infective action, though exhibiting it in a different way. This way may not need the breaching of the walls, but their scaling. I take the following from an unpublished manuscript which Dr. Lloyd Arnold of the Department of Pathology and Bacteriology, Chicago, has recently sent me:

'McCarrison has repeatedly called attention to the early appearance of digestive disturbances in vitamin deficiency studies. The pathological examination of the dead animals following avitaminosis experiments shows evidence of tissue changes due to infections of various kinds. We have found that one of the first demonstrable changes in avitaminosis is an alteration in the distribution of the bacterial life within the lumen of the intestinal tract. The bacteria ingested by the mouth are not destroyed in the usual manner, but remain viable for many hours within the contents of the whole length of the small intestine. The mixed bacterial flora of the large intestine ascend into the upper levels of the small intestine. There is a gradual and progressive loss of the power of the body surface to control the microbic life existing in contact with it. These findings have been constant, and hold for vitamin A, B, and D deficiencies. By the time the adult animals show a loss in body-weight, or the young animals show a stationary weight curve, there is evidence of bacterial invasion of the mucosa of certain surfaces. These latter observations have been made by numerous investigators. We attribute the early inflammatory changes in the lining membranes of the eye, mouth, throat, alimentary tract, etc., to the loss of power of these body-surface coverings to regulate the bacterial flora in contact with their cells. This precedes evidence of invasion of the membranes by bacteria.'

This statement, so amply demonstrated by Dr. Lloyd Arnold's investigations, calls to mind the contentions of Sir Arbuthnot Lane and Dr.

Nathan Mutch in regard to infection of the upper reaches of the intestine consequent on chronic gastro-intestinal stasis: a condition which, as my own researches (1921) have shown, may be due to the consumption of faulty food from the 'first bottle' onwards through life.

The function of vitamin A, so far as it is known at present, is thus to maintain the functional integrity of the cells covering body surfaces, thereby preventing invasion of the organism by microbic agents.

Here, however, I must re-emphasize the position, which I reached more than ten years ago and which all my subsequent work has but strengthened, that, whatever the specific function of any vitamin may be, vitamins are but links in the chain of essential substances requisite for the maintenance and harmonious regulation of the chemical processes in the tissues, and their action must be considered in connection with metabolism as a whole—that is, in relation to balance of food ingredients in general, to organs of digestion and assimilation, and to endocrine regulation of metabolism. Their deficiency, like that of other elements and complexes necessary for normal nutrition, leads to depreciation of cellular function; depreciation of cellular function is the foundation upon which disease is built (McCarrison, 1921).

V. SURGICAL DISEASES WHICH MAY BE ASSOCIATED WITH FAULTY NUTRITION

I find I have left myself little time to discuss specific diseases of surgical interest which may be associated with faulty nutrition. Mention may, however, be made of a few, illustrative of the several departments of surgery, but excluding the ophthalmic surgeon, to whose department some reference has already been made.

1. *Adenoids*

In the lantern-slide demonstration I showed examples of adenoid growths in the trachea. In rats these growths were the result of faulty feeding. It is no far cry from the trachea to the nasopharynx, where changes similar to those in the trachea of rats are so commonly found in children. And perhaps I might have found adenoids there also had my serial sections extended up to that situation. In work such as this it is constantly happening that one cannot do everything one wants to do, or that in looking for one thing one overlooks another. So whether or not rats do get 'adenoids' as the surgeon understands the term, I do not know, but they certainly get 'adenoid-like growths' in a region not far removed from the nasopharynx; and they get them because of faulty nutrition. And if in the trachea of rats, why not in the nasopharynx of children? The more so since Williamson and Pearse, and more recently Wollard (1931), have shown that the pharyngeal entoderm is an anatomical entity which embraces the lymphatic tissue of the nasopharynx and trachea. Evidence provided by the racial distribution of adenoids is not lacking to show that their occurrence may be related to faulty food. Thus Van der Bogert (1927) reports that Labrador Eskimos and those of Baffin Island who have been in contact with Western civilization, and whose food has changed accordingly, develop adenoids, whilst Polar Eskimos, whose diet has remained unchanged for centuries, do not. My own experience in rats would lead me to expect such a sequence of events.

2. *Otitis Media*

In rats one of the most common consequences of faulty food deficient in vitamin A is pus in the middle ear; its incidence may reach 60 or even 70 per cent. It is a condition of great frequency among school children in England and Wales, and, although its occurrence, as a sequel of certain diseases of childhood, is well known, the probable nutritional factor in its causation does not appear to me to have received the consideration it deserves. According to Hastings (1925) a high proportion of all cases occur before the fifth year, and many before the first birthday. In 1923 no fewer than 46,000 children had ear trouble; while 90 per cent of deafness in adults is due to preventable causes in childhood. Ponfick reported that of 100 necropsies in children under four, who died from various diseases, 91 showed evidence of middle-ear disease, and in only 10 of these was the trouble recognized during life. The causes giving rise to middle-ear disease interact with one another: they are squalid poverty—with its accompaniment of malnutrition—neglected catarrh, tonsils and adenoids, mouth-breathing, and the after-effects of measles, scarlet fever, and diphtheria. My rats do not suffer from the three last; but my experience in these animals leads me to believe that the insufficient supply of vitamin-A-bearing foods may be responsible for middle-ear disease in children to an extent much greater than is generally believed.

3. *Gastro-Duodenal Ulcer*

Twelve years ago (1919) I recorded the occurrence of this condition in guinea-pigs fed on a scorbutic diet of crushed oats and autoclaved milk. Recently I have repeated this experiment with the same result: and in this later experience I have found duodenal ulceration at all stages of the process up to perforation (in one case), the resulting abscess being localized. Magee, Anderson, and McCallum (1929) have observed similar conditions in calves fed on food deficient in certain essentials. Gastric and duodenal ulcer are extremely common in southern India, especially in South Travancore. The suggestion was made to me by Lieut.-Colonel E. W. C. Bradfield, I.M.S., late superintendent of the General Hospital, Madras, and by Dr. T. Somervell of the South Travancore Medical Mission, that the dietaries of the poorer classes, among whom these conditions were most common, might be concerned in their causation; an experiment was accordingly undertaken to put this view to the test.

Albino rats were used; and the experiment was continued for 675 days. Two diets were employed: one, resembling that eaten by the poorer class Madrassi, and containing rice, red pepper (chillies), tamarind, a little fish, and *conjee* (rice water); the other, resembling that of the poorer class Travancorian, and consisting largely of tapioca root, with rice, a little fish, red pepper, and rice water. Both these diets were very deficient, not only in vitamins of the A, B, and C classes, but in other regards also. The diets were prepared and cooked in the same way as by the people using them. It so happened that about the time this experiment matured I had occasion to examine at post-mortem some hundreds of well-fed stock rats who had lived through the same period of 675 days. In none of these was gastric or duodenal ulcer found. Among the rats fed on the Madrassi diet the incidence of gastric ulcer was 11·1 per cent, while the duodenum showed no signs of ulceration; among those fed on the Travancore diet, 27·7 per cent had gastric ulcer, and in 11·1 per cent of these the ulcers occurred both in the proximal (squamous) and in the distal (mucous) portion of the organ. No duodenal ulceration was found in animals fed on either diet, although in 11·1 per cent of those fed on the Travancore diet a marked duodenitis was present. The limitation of the ulceration to the stomach in rats was the more remarkable because the Travancorian diet is especially associated in man with duodenal ulcer. A further point of difference between the two groups was that while in animals fed on the Madrassi diet the ulcers were limited to the squamous portion of the organ, in those fed on the Travancorian diet the ulcers occurred for the most part in the mucous portion.

Here, then, is unequivocal proof that two diets in use by certain people in India are capable of causing peptic ulcer in albino rats. The high incidence of this condition among the human users of these diets may therefore be definitely attributed to this cause. As to the mechanism of ulcer production—that is another matter; the one that concerns me, as an investigator in the service of the Indian people, is that two of the diets used by them do cause peptic ulcer, while a third, on which my stock rats are fed, does not. For them the moral is unmistakable.

The excellent results reported by Harris (1928) in the treatment of gastric and duodenal ulcer by vitamin-rich food are in conformity with the findings in this experiment.

4. *Gynaecological Ailments*

The health of the womb and its appendages is dependent in various specific ways on the quality of the food. It is one of the sites in which faulty nutrition implants its seal, as has been shown, not only in the lower animals, but in the human being. The ovary, also, and the oviducts, may be affected in a similar way; while changes brought about in the bony framework of the pelvis may, as is well known (Stoney, 1930), be a fruitful cause of stillbirth and maternal mortality in childbirth. Fertility, the course of pregnancy, labour, resistance to infection following labour, and lactation may all be affected adversely by defects in quality of the food. It is said that 'nothing so predisposes to maternal death at confinement as an unhealthy womb' (Pearse and Williamson, 1931), and while imperfectly terminated pregnancies, aborted pregnancies, and other conditions may, and often are, the causes of this unhealth, faulty nutrition may also be concerned in it. Often I have seen deficiently-fed rats that die in pregnancy or at term from causes dependent on their faulty nutrition, and often also rats that come to term only to die with five or six foetuses in their wombs. Some of the anaemias of pregnancy so common in India are dietetic in origin—as the recent work of Dr. Lucy Wills has so conclusively shown. I make no claim that in human beings faulty nutrition is invariably a factor in the production of the tragedy of maternal mortality in child-birth, however frequently it may be so in rats. But here, as in other departments of medicine, experience in rats has pointed surely to means for the relief of suffering in mankind; and it might be well were we to accept this guidance more readily in regard to our women, and urge insistently that the mothers of our race be fed with knowledge and understanding.

5. *Lymph-adenoid Goitre and Graves' Disease*

A lecture might, by itself, be devoted to this subject, so much is the health of the thyroid gland and its departures from health associated with perfect nutrition on the one hand, and with faulty nutrition on the other. Lymph-adenoid goitre, originally described in man by Williamson and Pearse (1925), is 'the hypertrophic reaction of a physiologically inefficient organ with which there occurs a preponderance of lymphocytic aggregates, fibrosis, and a peculiar atrophy of the parenchyma.' I have produced it under experimental conditions in rats (McCarrison, 1927). In these animals the physiological inefficiency of the gland can be induced by faulty nutrition, but the exciting cause of the goitre is some positive factor which has so far escaped me. One cannot be sure when this type of goitre is going to occur; all that one can be certain of is that it surely will occur, in its own good time, provided the food is of a certain character. It is unrelated in its origin to iodine deficiency. I understand that it is now possible to diagnose this condition clinically in the human subject, and that thyroidectomy has been performed for its relief in not a few cases within recent years in London. Mention of its association with the use of foods deficient in vitamin A recalls the observation of Rabinowitch (1929) that a combination of relatively minute quantities of organic iodine, with a concentrated preparation of fat-soluble vitamins, causes as marked a lowering of the metabolic rate in Graves' Disease as larger doses of iodine when not combined with these vitamins. Fraser and Cameron (1929) have made a similar observation, using small amounts of sodium iodide instead of organic iodine. More recently, Abelin (1930) has demonstrated the great value of vitamin treatment in Graves' Disease.

'The hyperthyroid condition', he writes in his recent book, 'is one of the abnormal raising of the metabolic rate, together with a lowering of anabolic processes. This disorder of lowered activity of cells can be successfully combatted through nutrition. Among other things, for this purpose, the co-operation of vitamins is necessary. The organ destruction in thyrotoxicosis is caused by a vitamin poverty in the body. The need for vitamin supply is, therefore, increased in hyperthyroidism. Through plentiful use of vitamin-rich substances—cod-liver oil, egg-yolk, yeast, tomatoes, spinach, etc.—the great destruction of sugars has been reduced or almost completely overcome successfully in animal experiments.'

Again, it has lately been shown, in my own laboratory, how important is the balance between fat-soluble vitamins and iodine in the diet. The administration of iodine to rats fed on diets deficient in these vitamins may actually cause goitre (McCarrison, 1930). We have found, also, that the maintenance of an adequate iodine content in the thyroid gland is largely influenced by the content of vitamin C in the food (Sankaran, 1931). Few organs of the body, indeed none with the exception of the adrenals and thymus, are more profoundly affected by faulty nutrition than the thyroid gland, and few are more sensitive to this influence.

Deficiency Disease[1]

I. INTRODUCTION

The concept of 'deficiency disease' appears to have originated in the mind of the famous Dutch physician, Bachstrom, who, in his *Treatise on Scurvy*, published in 1734, attributed this malady to deficiency of something contained in fresh vegetable foodstuffs. It was not, however, until 162 years later (1896) that another Dutch physician—the late Dr. C. Eijkman—produced a deficiency disease (*polyneuritis gallinarum*) under experimental conditions; and not until 1901 that Professor Dr. G. Grijns, the revered President-General of this Congress, demonstrated that this 'disease, and by analogy most probably also beri-beri, was due to a deficiency—a partial hunger—a relative lack of certain still unknown substances, which can easily be destroyed for instance by moist heat, and which are distributed very unequally in the different articles of food, but cannot be omitted from food without serious harm to the nervous system. These substances (later called vitamins by Casimir Funk), which are present in the silver layer of rice, Grijns also found in other articles of food. . . . So Grijns was the first to set forth clearly what is justly to be called a deficiency disease and to study systematically the properties and distribution of a Vitamin.'

Appropriately enough, two other Dutch scientists—Jansen and Donath—were the first to isolate this vitamin in crystalline form, more than a quarter of a century later (1927). These discoveries, no less epoch-making than those of Pasteur and Lister, were the first trickle of a gradually swelling stream of knowledge which has spread over, permeated, refreshed and fructified the previously arid fields of Medicine. It is fitting that here, in the Capital City of their own country, we should acknowledge the debt which Modern Medicine owes to the Dutch physicians who made them.

It is remarkable that these discoveries were made, and that 'deficiency disease' had taken its place in the catalogue of human ailments, prior to the demonstration, by scientifically conducted investigations, that food was the paramount influence in determining man's general physical endowment, powers of endurance and of resistance to disease. Many, since the time of Hippocrates, had thought, or been convinced, it was, but no one, so far as I am aware, had proved it was. Hippocrates himself, in speaking of food and of its effects, had said: 'Whoever pays no attention to these things or paying attention does not comprehend them, how can he understand the diseases that befall a man?' And Louis Lemert, in the preface to his *Treatise of Foods*, published in 1704, remarked that 'If Foods contribute so necessarily to the preservation of life and health, they also produce the greatest part of those distempers, to which we are subject. . . .' But these, and other statements like them, were expressions of opinion only: they lacked proof. This proof appears to have first emerged from McCay's studies (1905–11) on the relation of food to the physique and health of Indian races; studies substantiated by my own observations among tribes of the Indian frontier (1902–11) and subsequently extended by experiment on animals.

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[1] Extract from number 150 in Bibliography.

The vast population of India is, as you probably know, made up of many different races, each having its own national diet: a diet evolved partly as a result of climatic and agricultural conditions and partly as a result of religious convictions. Some of these races, notably certain of them living in northern India, are unsurpassed, in perfection of physique, powers of endurance and of resistance to disease, by any other races of mankind. Others, notably the rice-eating races of the east and south, are of poor physique, low powers of endurance, and are subject to much disease. Such maladies as tuberculosis, leprosy, diarrhoea, dysentery, dental decay, gastric and duodenal ulcer, rheumatism, cancer, anaemia, rickets, beri-beri, diabetes, heart disease, ulcers, skin diseases and mental disease are more common—some of them much more common—among the people of the south than among those of the north of India. McCay's investigations were undertaken to find an explanation of these differences. Having taken all possible factors—heredity, endemic disease, climate, etc.—into consideration, he came to the conclusion that 'food was the all-important influence' in bringing them about. He laid special emphasis on the protein content of the diets of different races, attributing to it a paramount importance in determining the degree of physical endowment, powers of endurance and of resistance to disease exhibited by these races. This emphasis on one component of the diet, important though that component be, tended to obscure the greater truth revealed by his investigations: that of the paramount influence of food as a whole.

I approached the subject from a different angle: that of observing the effects—symptomatic, morbid anatomical and histopathological—on the animal organism of diets similar in constitution to those of Indian races whose physique and health differed so markedly. It may be said, at once, that I reached the same general conclusion as McCay. I found it possible not only to maintain suitable animals (monkeys, rats) in good health by feeding them, while living under conditions of perfect hygiene, on diets similar to those of races whose physique and health were of the best, but to produce a great variety of ailments—ailments to which human beings were subject—by feeding them on diets similar to those of races whose physique and health were poor or on modifications of Indian diets generally. These observations revealed what a properly constituted diet was and what combination of natural foodstuffs best served to maintain health. It was a diet made up of whole cereal grains, milk and its products, pulses, green leaf and root vegetables, fruit, and meat in the proportions adopted by the most vigorous and healthy of the races of India. This cardinal fact—the dependence of health on a diet composed of these natural foodstuffs, or of others of like nutritive value—seems to me to be a suitable, even necessary, starting-point from which to embark on the consideration of our subject. For it embraces all other facts dealing with the relations of constituents of food to health and of their deficiencies to disease.

II. FRAGMENTATION OF NATURAL FOODSTUFFS

The fragmentation of natural foodstuffs, by chemical, biochemical and biological methods is gradually revealing what the essential constituents of food are and why it is that a diet composed of these natural foodstuffs, in due proportion one to another, does maintain health, so far as food can maintain it. The limiting factor in this revelation, is, of course, the limitations of the methods employed to effect the fragmentation and to determine the role of each fragment in nutrition and its relation to organ, tissue, fluid or function of the body. A century ago, when these methods were still relatively crude, it had been shown that proteins, minerals, fats and carbohydrates were components of plant tissue and essential constituents of the food of man and animals. For many years these were thought to suffice for the growth, maintenance and energy requirements of the body, no doubt because no means existed, at that time, of detecting others. But with the introduction of new, and the perfecting of old, methods of fragmentation of natural foodstuffs, more and more of their constituents were found to be necessary for normal nutrition and, therefore, for normal health. When, for instance, Courtois (1812) discovered iodine it was soon associated with goitre, and Chatin (1850) propounded the theory that this disease was due to deficiency of iodine in the soil, plants and animal products of the regions affected. Baumann's discovery (1896) that iodine is an essential constituent of the thyroid gland provided a rational basis for this theory and led to the knowledge that the adequate ingestion and utilization of iodine is necessary for the maintenance of normal structure and function of the thyroid gland.

It was not, however, until Lunin (1884) introduced the biological method of food investigation that progress in the identification of the essential constituents of natural foodstuffs became rapid. The use of this method led to the discovery, initiated by the classical experiments of Eijkman and Grijns, of the vitamins whose numbers still go on increasing. It led also to recognition of the importance in nutrition of other components of natural foodstuffs: pigments, choline, certain amino acids and haemopoietic principles, for instance. It led to a renaissance of research on the mineral contents of foodstuffs, the results of which served to emphasize the importance of some and to reveal others whose essential character was not previously suspected or was greater than had been supposed. It revealed, moreover, or is revealing, the relations of these constituents of natural foodstuffs to one another and to structure and functions of organs and parts of the body. A brief reference to some of these relations is essential to my theme.

For some years following the discovery of vitamins these food factors had attached to them such limiting descriptive terms as 'anti-beri-beri', 'anti-neuritic', 'anti-scorbutic', 'anti-xerophthalmic', 'anti-rachitic', and 'anti-sterility': terms that have gradually fallen into desuetude, as research has continued to reveal new relations of these substances to organs, tissues, fluids and functions of the body. The importance of vitamin B_1 was found to lie not so much in its ability to prevent beriberi as in its relation to acts or processes involved in nutrition and to normal structure and functions of certain mechanisms of the body: as we now know, appetite, growth, lactation, carbohydrate metabolism, neuro-muscular, cardio-vascular and gastro-intestinal efficiency depend on its adequate supply and utilization, as does the normal functional activity of the adrenal glands, and of the nervous system, central as well as sympathetic. Vitamin A has been found to be something more than 'anti-xerophthalmic'. It is related in a specific way to structure and functions of epithelial tissues generally and is essential to normal vision, ovulation and the health of the nervous system. Its deficiency gives rise to a great variety of ailments consequent on disturbance of structure or function of epithelial tissues and of lowered resistance to local infection. Vitamin B_2 and its component parts have important relations to the skin, mucous membranes, gastro-intestinal tract, blood and nervous system. Vitamin C is something more than 'anti-scorbutic': it has an important part to play in the balanced chemistry of oxidation-reduction, is a constituent of structures at the intestinal threshold and of endocrine regulators of metabolism and maintains the integrity of intercellular cement substance, capillaries, teeth and gastro-intestinal tract. The controlling influence which vitamin D exercises over the metabolism of the very important mineral elements, calcium and phosphorus, lends to it a wider significance in nutrition than is suggested by the term 'anti-rachitic', and a relation to other tissues besides the bones and teeth. Vitamin E is no more an 'anti-sterility' factor than vitamin A: deficiency of the one interfering with placental function in females and germ-cell maturation in males, and that of the other with ovulation. Recent research credits vitamin E with a relatively selective neurotropic action, in the absence of which characteristic trophic degenerative changes arise in the nervous system and skeletal musculature. 'Vitamin F', or the unsaturated aliphatic acids so-called, is related to the reproductive process, vitamin K to the coagulation of the blood, and 'vitamin P' to capillary permeability. Certain pigments in natural foodstuffs are precursors of vitamins. Choline, present in small amounts in many plant and animal tissues, is concerned with the accumulation of fat in, and its dispersal from, the liver. Other constituents of natural foodstuffs—among them iron, copper, and a still unnamed factor—are necessary for normal haemopoiesis. Mineral constituents generally, among them several that are present in minute amounts, have profoundly important relations to growth structure and functions of the body into which I need not enter. Enough has been said to show that as the fragmentation of natural foodstuffs proceeds towards completeness more and more of their constituents are found to be related in specific ways to structure and/or functions of more and more organs and parts of the body. Skin and muscles; skeleton and teeth; mouth, gums, tongue and gastro-intestinal tract; nervous system and organs of special sense; heart and blood; lungs; endocrine, lymphatic and other glands; reproductive and urinary systems; even the mind itself—all these are affected adversely by food deficiencies of one kind or another. So it is that research has provided, or is providing, an explanation of the fundamental fact that a diet composed of natural foodstuffs, in proper proportion one to another, is the paramount influence in the maintenance of health. Few of us would wish to affirm that the fragmentation process is complete or that our knowledge of the relation of constituents of natural foodstuffs to organs, tissues, fluids and functions of the body is as yet other than rudimentary and unstable. It is all the more necessary, then, to adhere to the fundamental truth that a diet composed of natural foodstuffs, in due proportion one to another, contains all elements, complexes and qualities known and unknown, needed for normal nutrition, so far as food is capable of supplying them; provided always that these foodstuffs are produced on soils that are not impoverished. For in the application of this knowledge we have the means of greatly lessening man's infirmities without waiting for further discoveries.

III. CAUSES OF DEFICIENCY DISEASE

The causes of deficiency disease are those that interfere with the adequate supply or utilization of essential nutrients, increase the demand for them or give rise to their undue loss from the body. Poverty, ignorance, indifference, habit, non-availability of foodstuffs, faulty agricultural conditions, soil deficiencies, climate, sophistication of natural foodstuffs, faulty cooking, restricted diets in certain disease states, poor appetite; all these are factors which may be concerned in the inadequate supply or intake of food essentials. Gastric and intestinal disease, infestation by worms or operative interference with the stomach and duodenum may impair their utilization. Their supply or utilization may be inadequate to the demand for them or to the rate of their expenditure, as during growth, pregnancy, lactation, fever, operation, increased metabolic rate, and heavy muscular work. The stomach may fail to do its share in the production of haemopoietic or neuropoietic substances. One food essential may be deficient relative to another, one ineffective or harmful in default of another. Finally, there may be undue loss of essential nutrients as during menstruation, parturition, lactation, persistent vomiting and haemorrhage from any cause. Mention may be made here of salt deficiency due to excessive sweating and of water deficiency due either to inadequate supply or to excessive loss, as in severe vomiting and in choleraic states. All these factors of supply, demand, utilization, loss and imbalance, bave to be taken into consideration in connection with the genesis and maintenance of deficiency diseases. Inadequate supply of essential nutrients is the most important of them, though once gastro-intestinal disease is established utilization becomes a dominant factor. Inadequate supply may itself impair appetite and disturb gastric or intestinal function, thus interfering with intake or utilization of food essentials and producing a vicious circle.

Deficiencies of essential nutrients may be extreme or less extreme, complete or partial, absolute or relative, 'conditioned', multiple, exogenic or endogenic. Themselves negative factors in the production of disease, they may combine with positive factors—dietetic, microbic or toxic—to cause it. 'It is rare', as I wrote in 1921, 'that the food of human beings is totally devoid of any one vitamin; it is more usual for the deficiency to be partial, and for more than one vitamin to be partially deficient; it is more usual still for partial deficiency to be associated with deficiency of suitable protein and inorganic salts and with an excessive richness of the food in carbohydrates. Consequently, the manifestations of deficiency disease resulting from the faulty food are compounded of the several effects of varying degrees of avitaminosis on the one hand and of ill-balance of the food on the other. Nor is this all, for pathogenic organisms, present in the body during the period of subjection to the faulty food, contribute their share to the general morbid result . . . other factors, also, such as age, sex, individual idiosyncrasy, rate of metabolism, fatigue, cold, over-crowding, the varying susceptibilities of different individuals, of different organs, and of the same organs in different individuals, all play a determining part in the production of the morbid results of food deficiency.' Emphasis, based on experimental and histo-pathological studies, was thus laid for the first time on the importance in general medicine of partial degrees of avitaminosis and on the fact that vitamins had relations to organs, tissues and diseases other than those with which they were then associated by name—relations more important because of their bearing on disease in general.

Deficiency disease has now come to be regarded as part of the larger problem of 'dietetic malnutrition'; that is, disorder of the function of nutrition brought about by the inadequate supply or utilization of materials—particularly good protein, minerals and vitamins—needed for the growth, maintenance and repair of the body or its constituent parts and for the regulation of its processes. Faulty nutrition so induced has two main effects:

It leads to disturbance in structure or in functions of organs or parts of the body—disturbance varying with the nature and degree of the food fault or faults, with the age of the individual and with the length of time he is subjected to them; and it lowers the resistance of the body to infection. Thus, dietetic malnutrition acting alone or more often in conjunction with infection gives rise to degenerative change, to disability or to actual disease in great variety of form.

IV. SYMPTOMS AND SIGNS OF DIETETIC MALNUTRITION

The symptoms and signs of dietetic malnutrition are, accordingly, manifold: they have recently been summarized in a Report issued by the League of Nations; and my own experience justifies me in saying that the authors of this Report have not exaggerated them. They include: gastro-intestinal and pulmonary disease in artificially-fed infants, iron-deficiency anaemia, imperfect calcification of the developing teeth, rickets and osteoporosis, malformations of the bones, dental defects, abnormalities of the pharynx and poor growth and condition of the body generally. Consequent on dietetic malnutrition children have a lowered resistance to such diseases as measles, scarlet fever, bronchopneumonia, middle-ear disease, rheumatism and rheumatic diseases with their tragic associates—heart-disease and chorea. Increased tendency to fractures and their delayed healing, spinal curvatures, dental caries, deafness, running ears, nasal catarrh, septic tonsils, adenoids, inflamed eyes, defective vision, and nervous instability are also directly or indirectly due to dietetic malnutrition. Other effects of particular significance are those on the functions of the alimentary tract, to which I drew attention twenty years ago: diarrhoea, sprue-like condition, gastro-intestinal hypotonia, gastric catarrh, gastric ulcer, and colitis. Cardio-vascular derangement, lowered resistance to pulmonary infections, goitre, slow healing of wounds and of gastric ulceration, 'sub-clinical scurvy', macrocytic anaemias, pellagra, tetany, polyneuritis and subacute combined degeneration of the spinal cord, are other consequences of deficient intake, absorption or utilization of essential food factors.

In tropical countries there are in addition to diseases—beri-beri, scurvy, keratomalacia—produced by gross deficiencies many others due to those of lesser degree: poor growth and physical endowment, in the production of which calcium deficiency appears to play an important part, unhealth of the skin and its appendages, dermatitis and pellagra-like conditions, phrynoderma, petechial haemorrhages, oedema, stomatitis, angular stomatitis, sore tongue, gingivitis or spongy gums, gastro-intestinal ailments, night-blindness, xerophthalmia, anaemia, cardiac weakness, heat cramp, neuritis, pareses, dental decay, malocclusion and irregularities of the teeth, signs of rickets, osteomalacia, urinary calculus, gastric ulcer, and lowered resistance to infections in general and to intestinal and pulmonary infections in particular. Some of these, such as gastric ulcer and urinary calculus, are not yet generally recognized as of dietetic origin though my own researches have convinced me that they often are.

The detection of symptoms and signs of dietary deficiencies depends, like the detection of the essential nutrients present in natural foodstuffs, on the means available or adopted for their detection. These means are still inadequate though steady progress is being made in perfecting and adding to them. Proportionately to their increase and perfection new symptoms and signs of dietetic malnutrition are being, and will continue to be, found.

V. CONCLUSION

The newer knowledge of nutrition has revealed, and reveals the more with every addition to it, that a chief cause of the physiological decay of organs and tissues of the body is faulty food, wherein deficiencies of some essentials are often combined with excesses of others. It is reasonable, then, to assume that dietetic malnutrition is a chief cause of many degenerative diseases of mankind. However this may be, it seems clear that the habitual use of a diet made up of natural foodstuffs, in proper proportion one to another, and produced on soils that are not impoverished, is an essential condition for the efficient exercise of the function of nutrition on which the maintenance of health depends. This, combined with the proper exercise of the body and of its adaptive functions, is mankind's main defence against degenerative diseases: a bulwark, too, against those of infectious origin. Such, at least, is the conclusion to which my own studies in deficiency disease have led me.

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